URSODEOXYCHOLIC ACID THERAPY IN CHILDREN WITH CHOLESTATIC LIVER DISEASE*

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SUMMARY: Dinler G, Koçak N, Yüce A, Gürakan F, Özen H. (Gastroenterology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Ursodeoxycholic acid therapy in children with cholestatic liver disease. Turk J Pediatr 1999; 41: 91-98.

The beneficial effect of ursodeoxycholic acid have been documented in adults but experience with this agent is limited in the pediatric population. The objective of this study was to evaluate ursodeoxycholic acid treatment in children with cholestatic liver disease.

Twenty-four patients with intrahepatic cholestasis (neonatal hepatitis 7, Byler disease 7, idiopathic intrahepatic cholestasis 10) whose ages ranged from 1.5 months to 15 years were treated with ursodeoxycholic acid (15-20 mg/kg/day) for 12 months. Liver biopsy was performed initially on all patients and on 17 at the end of the twelve months. The outcome was evaluated by monitoring clinical and biochemical markers of cholestasis, including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, cholesterol, total serum fasting bile acids and total and conjugated bilirubin at entry and every three months of treatment.

Pruritus was ameliorated in all patients; there was complete disappearance of itching in 16.7 percent. There were significant decreases in mean serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin and gamma-glutamyl transpeptidase. Liver biopsy specimens showed a significant improvement in the cholestasis but not in fibrosis. No adverse effects of therapy were noted.

The improvements in the clinical and biochemical parameters and tolerability of the drug suggest that ursodeoxycholic acid is a safe and effective treatment in children with intrahepatic cholestasis. *Key words: children, ursodeoxycholic acid, cholestatic liver disease.*

Over the last few years, several clinical studies proposed that ursodeoxycholic acid (UDCA) was beneficial in the treatment of a variety of cholestatic liver diseases both in adults and children[1-6]. Parenchymal damage in cholestatic liver disease is thought to be due to intrahepatic accumulation of toxic bile acids[4]. At least 50 percent of these toxic bile acids are hydrophobic. If untreated, patients may eventually progress to severe biliary cirrhosis with portal hypertension and liver failure. Therefore, changes in the hydrophobic-hydrophilic balance of the bile acid pool, with the aim of increasing its hydrophilicity by exogenous administration of

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hydrophilic bile acids like UDCA, may be beneficial[3-5]. Ursodeoxycholic acid, (UDCA), a tertiary bile acid, is more efficiently absorbed from the ileum than the other bile acids. It is less toxic than the other bile acids for hepatocytes and is also a choleretic agent. Direct hepatoprotective effect, cholehepatic shunt mechanism and immune modulating effects may also be important[7-9]. With the exogenous UDCA therapy, intestinal absorption of endogenous bile acids decreases, and concentrations of these endogenous bile acids in the bile acid pool decline. Ursodeoxycholic acid (UDCA) replaces these bile acids and increases total bile acid pool[7-9]. Therefore, enrichment of the circulating bile acid pool with hydrophilic UDCA may improve cholestatic liver disease.

The beneficial effects of UDCA have been documented in adults with cholestatic liver diseases such as primary biliary cirrhosis and sclerosing cholangitis, but experience with this drug in pediatric patients is limited. We prospectively evaluated the efficacy and tolerance of a long-term administration of UDCA in pediatric cholestatic liver diseases.

Material and Methods

Children with cholestatic liver disease evaluated between January 1994 and December 1995 were enrolled in the study. Patients with extrahepatic biliary abnormalities were excluded. The diagnosis was based on typical clinical symptoms such as pruritus, jaundice and laboratory findings of elevated conjugated bilirubin (≥ 1 mg/dl), total serum bile acids (≥ 15 μmol/L), alkaline phosphatase (AP) (≥ 50 IU/L) and histological features of cholestasis. Twenty-seven patients fulfilled the above criteria, 24 of whom completed a 12-month course of treatment. Their ages were between 1.5 months and 15 years (mean 39.7 ± 48.0 months, median 21 months); 11 were below 12 months of age. Two were lost to follow-up and one died at the third month of treatment. Seven of the patients were diagnosed as neonatal cholestatic hepatitis (3 cytomegalovirus hepatitis, and 4 idiopathic neonatal hepatitis). Seven patients were diagnosed with Byler disease because of the presence of positive family history, chronic cholestasis, severe pruritus and normal serum gamma-glutamyl transpeptidase (GGT) levels with elevated total serum bile acids and bilirubin[10]. No cause could be found in the remaining 10 patients (3 cirrhosis, 1 chronic active hepatitis, 6 chronic cholestatic hepatitis histologically), and they were regarded as idiopathic intrahepatic cholestasis (IIHC). Parents were given a description of the study and informed consent was obtained.

Prior to starting the treatment, the conventional liver function tests [alanine transaminase (ALT), aspartate transaminase (AST), total and conjugated bilirubin, GGT, AP, cholesterol, and prothrombin time] were all carried out by routine laboratory methods. Serum was tested for markers of viral infections (hepatitis

A, B, C, CMV, rubella) and autoimmunity. Serum α-1 antitrypsin level and sweat chloride concentration were also measured. Abdominal ultrasonography was done on all patients and hepatobiliary scintigraphy, when indicated. Total serum bile acid concentrations were measured by the 3α-hydroxysteroid dehydrogenase method[11].

A liver biopsy was performed on all patients within one month prior to therapy. Ursodeoxycholic acid (UDCA) (Ursofalk, Falk Co, Germany) was administered orally at doses of 15-20 mg/kg/day, divided into two doses, for 12 months in 24 patients, Physical examination and conventional liver function tests were carried out every three months. Follow-up liver biopsy was possible in 17 patients after 12 months of treatment. Other parents refused the second biopsy.

Friedman two-way ANOVA was used for repeated measures to analyze the changes in serum liver enzyme levels and changes in bile acid concentrations[12]. Values are expressed as mean ± standard deviation (SD) and a two-tailed p value < 0.05 was considered significant.

Results

At presentation jaundice was seen in 21 patients (87.5%) (8 IIHC, 7 neonatal hepatitis, 6 Byler disease) and a history of recent jaundice was obtained in the remaining three patients. Eighteen patients (75.0%) (4 neonatal hepatitis, 7 Byler disease and 7 IIHC) suffered from pruritus. Fourteen patients (58.3%) had acholic stools and 10 patients (41.7%) had abdominal distention. All patients had hepatomegaly and 19 (79.2%) also had splenomegaly.

Pruritus was ameliorated in all patients, and disappeared completely in three (7 IIHC, 1 Byler disease). Jaundice resolved in 71.4 percent of the patients. Three patients with IIHC, two with Byler disease and one with neonatal hepatitis were still icteric at the end of treatment. Stool color became normal in all patients with acholic stools. Hepatomegaly disappeared in four (16.7%) and reduced in size in 12 (50%). Splenomegaly disappeared in four (21.1%) patients and decreased in size in six (31.6%). Reduction of hepatomegaly and splenomegaly was confirmed by physical examination and ultrasound scanning.

Serum AST and ALT levels were high in 22 (91.7%), total bilirubin levels in 21 (87.5%), AP phosphatase in 16 (66.7%), GGT in 13 (54.2%), cholesterol in 12 (50.0%), and prothrombin time in six (25.0%) patients before the treatment. Prothrombin time became normal after vitamin K administration in all patients.

Effects of UDCA therapy on routine laboratory tests are summarized in Table I. The mean serum concentrations of ALT, AST, AP, GGT, and bilirubin fell significantly. Cholesterol values decreased slightly. There were no significant changes in total serum bile acids. However, at the end of treatment ALT, AST, AP, GGT and bilirubin levels were still abnormal in 10, 10, 12, eight and six

patients, respectively. Biochemical parameters continued to improve during the second six months of therapy. There were no improvements in clinical and biochemical findings in patients with cirrhosis.

Table I: Mean Concentration Values of Liver Function Tests Before and After Six and Twelve Months of UDCA Therapy (mean ± SD)

Tests (Normal Range)	Before UDCA	After 6 Months	After 12 Months	p Values
ALT (< 50 IU/L)	174.2 ± 148.4	137.1 ± 148.4	93.3 ± 115.5	0.0038
AST (< 50 UI/L)	247.0 ± 233.8	128.9 ± 125.2	96.2 ± 82.8	0.0006
AP (< 400 IU/L)	805.2 ± 703.9	397.0 ± 186.3	493.8 ± 256	0.0008
GGT (< 35 IU/L)	319.1 ± 727.6	83.6 ± 126.1	67.0 ± 98.8	0.0129
Total bilirubin (< 1.2 mg/dl)	7.1 ± 7.8	1.8 ± 2.7	1.6 ± 2.7	0.0000
Bile acids (< 15 µmol/L)	238.3 ± 201.3	185.9 ± 279.6	206.7 ± 248.1	0.8883
Cholesterol (< 200 mg/L)	223.8 ± 91.7	157.3 ± 60.2	165.2 ± 87.0	0.0709

If neonatal hepatitis, Byler disease and IIHC were considered separately, patients with neonatal hepatitis showed improvements in all biochemical parameters, but a significant decrease was present in AP and bilirubin values (Table II). ALT and AST levels were high in all seven patients at the beginning and normalized in four of them at the end of 12 months of therapy. Bilirubin levels were high in all patients at the beginning and normalized in six. Cholesterol, AP and GGT levels were high in five, five and six patients, respectively, before therapy, and high levels continued in three, two and one patients, respectively, at the end.

Table II: Biochemical Parameters Before and After Six and Twelve Months of UDCA Therapy in Patients with Neonatal Hepatitis (men ± SD)

Tests (Normal Range)	Before UDCA	After 6 Months	After 12 Months	p Values
ALT (< 50 IU/L)	293.8 ± 175.5	252.4 ± 402.2	118.1 ± 153.4	0.3679
AST (< 50 UI/L)	449.2 ± 305.3	196.5 ± 198.1	110.2 ± 87.2	0.1801
AP (< 400 IU/L)	1145 ± 1136	538.4 ± 266.4	416.4 ± 184.0	0.0498
GGT (< 35 IU/L)	765.1 ± 123.5	150.0 ± 229.2	87.3 ± 160.9	0.4493
Total bilirubin (< 1.2 mg/dl)	11.9 ± 10.7	2.7 ± 4.4	1.9 ± 3.8	0.0388
Bile acids (< 15 µmol/L)	226.8 ± 115.9	269.6 ± 316.8	205.6 ± 252.4	1.000
Cholesterol (< 200 mg/L)	232.0 ± 61.4	158.7 ± 91.7	173.2 ± 103.7	0.1738

In patients with Byler disease, only AST concentrations decreased significanty, whereas ALT, bilirubin, AP, GGT and cholesterol concentrations only slightly decreased (Table III). All patients had high levels of ALT and AST, which persisted in only two at the end of therapy. While bilirubin and AP levels were abnormal in six and five patients, respectively, at the beginning, they remained high in two and four at the end. Cholesterol levels normalized in both patients with high levels.

Table III: Biochemical Parameters Before and After Six and Twelve Months of UDCA Therapy in Patients with Byler Disease (men ± SD)

Tests (Normal Range)	Before UDCA	After 6 Months	After 12 Months	p Values
ALT (< 50 IU/L)	126.7 ± 136.2	83.5 ± 72.3	85.2 ± 138.6	0.1561
AST (< 50 UI/L)	166.1 ± 172.2	87.2 ± 46.3	79.1 ± 88.8	0.0595
AP (< 400 IU/L)	551.8 ± 145.1	389.8 ± 69.5	527.0 ± 136.0	0.1738
GGT (< 35 IU/L)	20.8 ± 11.5	15.5 ± 6.5	14.0 ± 4.1	0.5134
Total bilirubin (< 1.2 mg/dl)	7.7 ± 8.2	2.1 ± 2.3	2.2 ± 3.2	0.1738
Bile acids (< 15 µmol/L)	462.3 ± 307.2	261.0 ± 444.9	355.0 ± 371.9	0.8187
Cholesterol (< 200 mg/L)	181.1 ± 71.3	126.8 ± 26.2	136.5 ± 40.4	0.2122

In patients with IIHC, biochemical values improved significantly, with the exception of serum bile acid and cholesterol levels (Table IV). Among 10 IIHC patients, ALT, AST and bilirubin levels were high in eight initially and were still high in five, five and three of them, respectively, at the end. Alkaline phosphatase GGT and cholesterol levels were abnormal in six, seven and five patients respectively, at presentation, and were still high in five, six and one at the end of treatment.

Table IV: Biochemical Parameters Before and After Six and Twelve Months of UDCA Therapy in Patients with Idiopathic Cholestasis (men ± SD)

Tests (Normal Range)	Before UDCA	After 6 Months	After 12 Months	p Values
ALT (< 50 IU/L)	161.7 ± 134.6	93.9 ± 65.7	81.7 ± 70.1	0.0450
AST (< 50 UI/L)	162.0 ± 113.6	110.7 ± 84.8	98.4 ± 82.5	0.0450
AP (< 400 IU/L)	744.4 ± 497.0	303.0 ± 112.8	524.9 ± 355.9	0.0017
GGT (< 35 IU/L)	192.5 ± 102.3	99.6 ± 79.8	95.1 ± 59.7	0.0313
Total bilirubin (< 1.2 mg/dl)	3.4 ± 1.9	0.9 ± 0.6	1.0 ± 0.8	0.0006
Bile acids (< 15 µmol/L)	121.6 ± 103.1	106.5 ± 135.8	125.1 ± 126.6	0.9726
Cholesterol (< 200 mg/L)	257.8 ± 124.6	206.3 ± 33.5	200.6 ± 119.2	0.0970

None of the patients with normal biochemical values initially showed abnormalities during the treatment period, nor did biochemical values deteriorate in any of the patients after reaching normal levels at six months.

Before the treatment all but one biopsy material showed fibrosis. Cellular and canalicular cholestasis was evident in 21 specimens. After 12 months of treatment there was a complete disappearance of cholestasis in 70 percent and diminution in 20 percent of 17 specimens evaluated. There was no change in fibrosis. Ursodeoxycholic acid (UDCA) was well tolerated and compliance was good in all patients. No adverse effects were noted.

Discussion

There is no effective medical treatment for intrahepatic cholestasis. Recently, UDCA has been proposed as a possible treatment modality for a variety of cholestatic liver diseases. The mechanism by which UDCA affects liver functilon tests has

not been clearly established. Parenchymal damage in cholestatic liver disease is thought to be due to the intrahepatic retention and accumulation of toxic bile acids. Ursodeoxycholic acid (UDCA) may reduce the toxicity of endogenous bile acids by competitively inhibiting their absorption from the intestine, thereby reducing their concentration and increasing hydrophilic bile acid concentrations[1-4]. The UDCA supplementation markedly increases the relative proportions of UDCA in the bile acid pool[3, 4]. The intake of hydrophilic bile acid reduced the proportion of the hepatotoxic hydrophobic compound. In our study, initial serum bile acid levels mildly decreased at the sixth month of therapy and increased at the end. As only total bile acid levels could be measured, we could not determine the composition of the bile and proportion of UDCA.

Most of the studies have involved adult patients with various chronic liver diseases such as primary biliary cirrhosis, chronic active hepatitis, primary sclerosing cholangitis, and benign recurrent intrahepatic cholestasis[1, 8]. Studies with UDCA in pediatric patients are limited and the majority of them are related to children with cystic fibrosis[3, 13, 14]. Our study was planned to determine the effects of UDCA in children with intrahepatic cholestasis of different etiologies.

Jaundice, a prominent symptom, disappeared in the majority of the patients. The most devastating symptom of cholestasis is pruritus, for which UDCA is one of the administered medications. Pruritus completely disappeared in 16.7 percent and was ameliorated in all our patients. In their preliminary report, Balistreri et al.[15] also found a marked decrease in pruritus in 60 percent of patients with intrahepatic cholestasis, but they only studied five patients. Similar results were reported in adult patients with primary biliary cirrhosis[2, 4].

The majority of the studies have focused on the effect of UDCA on symptoms and biochemical parameters, but reports on the effects on liver and splen size are scarce. In our study, hepatomegaly disappeared in 16.7 percent and reduced in size in half of the patients; changes in splenomegaly were also seen. In a recent report by Spagnuolo et al.[16], UDCA (30 mg/kg/day, divided into 3 doses) was administered to seven children with total parenteral nutrition-related cholestatic liver disease. All patients had hepatomegaly and six had splenomegaly. Reduction of hepatomegaly and splenomegaly was observed within two weeks of the onset of UDCA administration. In our cirrhotic patients no improvement was noted. This effect seems to depend on the degree of liver damage, as no change in liver and spleen size was observed in patients with primary biliary cirrhosis in another study[2]. Ursodeoxycholic acid (UDCA) may have a beneficial effect in the early stages of the liver disease.

The most predominant effect of UDCA therapy was shown on biochemical parameters. This might reflect an amelioration of liver function. Liver function tests, including AST, ALT, AP, GGT and bilirubin concentrations, improved significantly

after UDCA administration in patients with primary biliary cirrhosis[2, 4], cystic fibrosis with concomitant chronic liver disease[3, 13, 14], chronic active hepatitis caused by hepatitis B and C viruses[5], and with extrahepatic biliary atresia and chronic intrahepatic cholestasis[15, 17]. UDCA-related improvement in liver function tests is dose dependent, at least in cystic fibrosis[14]. We did not evaluate the effect of dose on liver function tests. It has also been shown that improvement continues with treatment and that rebound effects may be seen after discontinuation of therapy[2, 5, 16]. In our study, the mean serum concentrations of ALT, AST, bilirubin, AP, and GGT fell significantly. Although it was not statistically significant, the mean concentrations of cholesterol also decreased. Decreases in beochemical parameters occurred during the sixth month of therapy and persisted throughout the study. Treatment with UDCA for one year led to marked improvement in serum liver tests and, once normal values were obtained, no deteroriation was noted. Although the number of the patients was small, we observed the positive effect of UDCA in different diseases. More parameters were found to improve in patients with IIHC. Our results show that continuation of UDCA therapy after six months increases improvement in parameters. It was also shown that the proportion of patients recovering clinically increased with prolonged therapy[2, 4]. We did not observe any adverse effects and all patients tolerated the drug well.

Another question is whether UDCA treatment may alter the liver histology. After 12 months of treatment, cellular and canalicular cholestasis disappeared or decreased in 90 percent of our patients. We did not observe any change in fibrosis. None of the patients showed complete recovery in liver histology. The duration of follow-up in our study may not have been enough to see improvement in hepatic fibrosis, but Leuschner et al.[2] showed histological improvement in only three of 22 patients after four to 12 years of treatment. Poupon et al.[4] also showed significant improvements in the mean histologic features, except for fibrosis, similar to our study. The patient groups in the last two studies were primary biliary cirrhosis. Although Ikeda et al.[18] observed beneficial clinical effects of additional colchicine administration in UDCA-treated patients with primary biliary cirrhosis, they did not mention histologic changes. We had previously shown that long-term colchicine treatment alone did not affect hepatic fibrosis[19]. We did not try it together with UDCA.

Although our study represent only a preliminary and uncontrolled investigation, the results suggest that administration of UDCA leads to clinical and biochemical improvement in cholestatic liver disease in children. Ursodeoxycholic acid (UDCA) also improves cholestasis, but not fibrosis, histologically. A larger-scale controlled study is needed to show the effects on liver function, histology and survival in patients with cholestatic liver disease. This improvement in clinical and laboratory parameters and absence of side effects suggest that UDCA is a safe and effective drug for childhood cholestatic liver disease. It improves the quality of life of the patients and may be given as long as the disease continues.

REFERENCES

1. Cirillo NW, Zwas FR. Ursodeoxycholic acid in the treatment of chronic liver disease. Am J Gastroenterol 1994; 89: 1447-1452.
2. Leuschner U, Güldütuna S, Imhof M, Hübner K, Benjaminov A, Leuschner M. Effects of ursodeoxycholic acid after 4 to 12 years of therapy in early and late stages of primary biliary cirrhosis. J Hepatol 1994; 21: 624-633.
3. Merli M, Bertasi S, Servi R, et al. Effect of a medium dose of ursodeoxycholic acid with or without taurine supplementation on the nutritional status of patients with cystic fibrosis: a randomized, placebo-controlled, crossover trial. J Pediatr Gastroenterol Nutr 1994; 19: 198-203.
4. Poupon RE, Balkau B, Eschwège E, Poupon R. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. UDCA-PBC Study Group. N Engl J Med 1991; 324: 1548-1554.
5. Rolandi E, Franceschini R, Cataldi A, Cicchetti V, Carati L, Barreca T. Effects of ursodeoxycholic acid (UDCA) on serum liver damage indices in patients with chronic active hepatitis. A double-blind controlled study. Eur J Clin Pharmacol 1991; 40: 473-476.
6. Poupon R, Chrètien Y, Poupon RE, Ballet F, Calmus Y, Darnis F. Is ursodeoxycholic acid an effective treatment for primary biliary cirrhosis? Lancet 1987; 1: 834-836.
7. Hofmann AF. Pharmacology of ursodeoxycholic acid, an enterohepatic drug. Scand J Gastroenterol 1994; 204 (Suppl): 1-15.
8. Van de Meeberg PC, van Erpecum KJ, van Berge-Henegouwen GP. Therapy with ursodeoxycholic acid in cholestatic liver disease. Scand J Gastroenterol 1993; 200 (Suppl): 15-20.
9. Crosignani A, Podda M, Batrezatti PM, et al. Changes in bile acid composition in patients with primary biliary cirrhosis induced by ursodeoxycholic acid administration. Hepatology 1991; 14: 1000-1007.
10. Alonso EM, Snover DC, Montag A, Freese DK, Whitington PF. Histologic pathology of the liver in progressive familial intrahepatic cholestasis. J Pediatr Gastroenterol Nutr 1994; 18: 128-133.
11. Fawo O. Quantitative determination of serum bile acids using a purified 3α-hydroxysteroid dehydrogenase. Scand J Gastroenterol 1975; 10: 747-755.
12. Dawson-Saunders B, Trapp RG (eds). Basic and Clinical Biostatistics (2nd ed). Connecticut: Appleton and Lange; 1994.
13. Colombo C, Setchell KD, Podda M, et al. Effects of ursodeoxycholic acid therapy for liver disease associated with cystic fibrosis. J Pediatr 1990; 117: 482-489.
14. Colombo C, Crosignani A, Assaisso M, et al. Ursodeoxycholic acid therapy in cystic fibrosis-associated liver disease: a dose response study. Hepatology 1992; 16: 924-930.
15. Balistreri WF, Heubi JE, Whitington P, Perrault J, Bancroft J, Setchell KD. Ursodeoxycholic acid (UDCA) therapy in pediatric hepatobiliary disease. Hepatology 1989; 10: A602.
16. Spagnuolo MI, Iorio R, Vegnente I, Guarino A. Ursodeoxycholic acid for treatment of cholestasis in children on long-term total parenteral nutrition: a pilot study. Gastroenterol 1996; 111. 716-719.
17. Ullrich D, Rating D, Schröter W, Hanefeld F, Bircher J. Treatment with ursodeoxycholic acid renders children with biliary atresia suitable for liver transplantation. Lancet 1987; 2: 1324.
18. Ikeda T, Tozuka S, Noguchi O, et al. Effects of additional administration of colchicine in ursodeoxycholic acid treated patients with primary biliary cirrhosis: a prospective randomized study. J Hepatol 1996; 24: 88-94.
19. Koçak N, Yüce A, Gürakan F, et al. Colchicine in the treatment of hepatic fibrosis in children. Am J Gastroenterol 1996; 91: 179-180.