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Preventive Effect of Ursodeoxycholic Acid on Parenteral Nutrition-Associated Liver Disease in Infants

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SUMMARY

Introduction Parenteral nutrition-associated cholestasis is well recognized phenomenon in the term and preterm infant receiving long-term parenteral nutrition.

Objectives The aim of this study was to evaluate the effect of ursodeoxycholic acid (UDCA) use on cholestasis in newborns on prolonged TPN.

Methods A total of 56 infants were enrolled in this retrospective study: control group consisted of lower (1500 g) birth weight infants (n=30), as well as the group of pediatric (n=11) and surgical patients (n=15) treated with UDCA. Blood chemistries were obtained two times weekly.

Results All of 56 newborns developed cholestasis but duration of parenteral nutrition (PN) before onset of cholestasis was significantly longer in UDCA treated patients. Average duration of PN before the onset of cholestasis in control group of patients was 25 days in distinction from treated pediatric and surgical patients (39 and 34 days, respectively). The peak serum conjugated bilirubin (CB), AST, ALT and alkaline phosphatase (AP) levels were significantly lower in the treated groups. There was no significant difference among treated pediatric and surgical patients and between lower and higher birth weight infants considering the CB, ALT, AST and AP peak. Duration of cholestasis was significantly decreased in all treated groups. There was a significant difference in time needed to achieve complete enteral intake between pediatric and surgical patient group.

Conclusion Cholestasis developed significantly later in treated groups than in the controls. UDCA appears to be very successful in reducing the symptoms of cholestasis. The difference in efficacy of UDCA treatment between lower and higher birth weight infants could not be proven.

Keywords: parenteral nutrition; cholestasis; infants; ursodeoxycholic acid

INTRODUCTION

Successful development of total parenteral nutrition (TPN) has revolutionized the outcome for neonates and infants with intestinal failure from either congenital abnormalities or extensive gastrointestinal surgery [1]. Parenteral nutrition-associated cholestasis (PNAC) is a dangerous and well recognized phenomenon in the term and preterm infant receiving long-term parenteral nutrition. The incidence is relatively high and varies from 7.4% to 84% [1, 2]. In a period of about 20 years, a decline in TPN cholestasis has been noticed [3, 4]. Its exact mechanism of origin is unclear and multifactorial [5]. The pathogenesis is related to immaturity, prolonged enteral starvation, early and prolonged PN, bacterial infection, sepsis, hypoxia, major surgeries, liver toxicity of amino acids and their products of photo oxidation, hyper-manganesemia and pollution of infusion solutions [2]. Abnormal bile saturation has been observed as a result of decreased enterohepatic circulation, and poorer ileal reabsorption of bile salts [6]. UDCA is a hydrophilic dihydroxylated bile acid that has been widely used in various chronic cholestatic liver diseases [7, 8, 9]. In clinical practice, many infants are treated with UDCA, but data regarding its efficacy are limited. Limited case studies and uncontrolled trials have suggested that UDCA leads to improvement in TPN-associated cholestasis in infants, children, and adults [1, 2, 10, 11]. There have been limited data on the effects of UDCA for PNAC very-low-birth-weight (VLBW) infants; however, first studies encourage [7, 12].

OBJECTIVE

The aim of this study was to evaluate the effect of ursodeoxycholic acid (UDCA) use on cholestasis in newborns on prolonged TPN. The purpose of this investigation was to test the following hypothesis: UDCA when given prophylactically to infants receiving TPN will lead to lower peak serum conjugated bilirubin

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(CB) levels. Infants of lower birth weight (less than 1500 g) receiving long-term TPN, who have a significantly greater risk of developing TPN-associated cholestasis, will have higher benefit from therapy with UDCA as assessed by peak CB levels compared with the infants with higher birth weight and shorter duration of TPN. In addition, the aim of this study was to determine the difference between the efficacy of UDCA in pediatric and surgical patients.

Table 1. Distribution of infants in the study groups

Groups	BW (g)	N
Control group	<1500	15
	>1500	15
Pediatric patients treated with UDCA	<1500	5
	>1500	6
Surgical patients treated with UDCA	<1500	9
	>1500	6

UDCA – ursodeoxycholic acid; BW – body weight; N – number of patients

METHODS

This study was a retrospective-bicentric trial to assess whether UDCA can prevent or reduce the severity of TPN-associated cholestasis. During five-year period, all infants who fulfilled the following inclusion criteria: TPN for >2 weeks, serum initial CB<2 mg/dL (34.2 μmol/l), and a negative diagnostic workup for other possible causes of jaundice were enrolled in the study. There were no restrictions placed on birth weight, gestational age and sex.

Baseline screening laboratories were obtained, including liver biochemical tests: serum total and conjugated CB, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP) gamma-glutamyl transaminases (GGT) and bile acids (BA) levels. PN was initiated in all infants using solutions that contained 10% dextrose, 6,5% amino acids (Vaminolact-Fresenius Kabi), 20% lipid solution (Intralipid-Fresenius Kabi), electrolytes, trace elements (Peditrace, Fresenius Kabi), minerals and vitamins via the peripheral or central vein within three days after birth. All authors agree that no side effects were noticed when UDCA was administered in a dose of 30 mg/kg/day [2, 7, 12, 13, 14]; therefore, in our study, UDCA 30 mg/kg/d (Ursofalk syrup 10 mg/ml) divided in three daily doses was given by mouth, via nasogastric tube or gastrostomy tube as soon as the gastrointestinal tract was able to use it. A parallel placebo group was evaluated for comparison.

Blood chemistries (ALT, AST, GGT, AP, CB, BA) were obtained two times weekly. Serum CB (direct bilirubin) level is a measure of development and severity of TPN-associated cholestasis [15]. Cholestasis was defined as the presence of an elevated serum CB level more than 2 mg/dl. Increased GGT is a specific parameter of bile duct obstruction. However, the problem in interpretation is that the level of GGT is already elevated in premature babies. Children's hepatobiliary tree was also examined ultrasonographically. Possible presence of biliary sludge, cholelithiasis, choledocholithiasis and intrahepatic biliary dilatation was also examined.

Indications for TPN were as follows: prematurity (pediatric subjects) and NEC, gastroschisis, severe jejunoileal atresia, loss equal to or exceeding 50% of the expected small bowel length for the given gestation age (surgical subjects). Exclusions included multiple congenital abnormalities, life-threatening renal or cardiovascular disease, evidence of biliary tract abnormalities or evidence of other forms of cholestatic liver disease. Investigation to rule out other possible causes of jaundice, including sepsis test, blood cytomegalovirus IgM test, urine virus isolation, newborn screen (thyroid stimulating hormone, galactosemia, glucose-6-phosphatase deficiency, congenital adrenal hyperplasia and phenylketonuria) and abdominal ultrasonography finding as well as urine examination for reducing substances, alfa-1-antitrypsin phenotype, and sweat chloride was performed based on individual case presentations.

This investigation was reviewed and approved by the Institutional Review Committee from each of the participating institutions and by a parent and/or guardian of the infant.

Comparisons between the groups were performed using analysis of variance (ANOVA) and consequently least significant difference (LSD) test, if appropriate.

RESULTS

Our investigation included six groups of patients. Control group consisted of lower (1500 g) birth weight infants, as well as the group of pediatric and surgical patients treated with UDCA (Table 1). For the entire group of investigated infants, there were no significant differences in Apgar score, total duration of TPN or age at onset of TPN between the UDCA-treated and control subjects. There was no significant difference among groups in the initial serum levels of total and CB. Therefore, the risk of PNAC was comparable in all groups. Age at initiation of enteral feeds was significantly earlier in pediatric patients no matter of body weight (BW) in comparison with the surgical patients or control group. The age of achieving full feeds was significantly different among control group and treated groups, especially between the controls under 1500 g BW and treated pediatric patients under 1500 g BW, probably because of the physiological differences in normal values within the first weeks of life. There was no significant difference of peak direct bilirubin, peak ALT, AST and AP between treated pediatric and surgical patients. There was statistically significant difference in time needed to achieve complete enteral intake between pediatric and surgical group (Table 2). No patient in this study developed hepatic failure or mortality. No side-effects (e.g., diarrhea) were noted.

DISCUSSION

PN has been associated with hepatobiliary complications. Hepatic dysfunction secondary to TPN differs in adults

Table 2. Clinical features and peak serum biochemistry values presented as mean ± standard deviation

Variables	Control group		Treated pediatric patients			
	BW<1500 g (n=15)	BW>1500 g (n=15)	BW<1500 g (n=5)	BW>1500 g (n=6)	BW<1500 g (n=9)	BW>500 g (n=6)
Gestational age (weeks)	29.60±2.32	35.33±1.88	27.40±2.51	37.50±1.64**	28.56±2.19	37.17±2.04
Birth weight (g)	1161.67±211.61	2521.53±458.12	817.00±106.17	2888.33±807.33	1025.00±150.50	3193.33±840.52**
Onset of cholestasis (age in days)	31.00±6.05	30.63±3.70	39.50±2.12*	40.67±4.16**	40.20±2.86*	40.50±7.14**
Fasting duration (age in days)	23.13±6.16	15.16±3.16	11.20±2.59*	14.67±5.05	17.89±5.06*,†	22.33±6.47**,‡
Age to tolerate full feeds (days)	35.67±10.22	29.87±5.36	22.40±5.94*	26.67±6.86	28.33±8.77†	43.60±6.54**,‡
Duration of PN before onset of cholestasis (days)	26.63±8.93	24.62±7.09	36.50±4.28*	36.00±8.16**	38.00±6.39*	33.25± 5.97**
Total duration of PN	30.67±9.85	27.67±5.25	23.00±17.38*	29.50±11.29	28.78±13.74†	37.60±6.66**,‡
Duration of cholestasis (days)	68.54±16.01	72.50±24,58	27.50±10.20*	34.67±8.95**	36.60±27,38*	43.25±15.47**
Initial direct bilirubin (mg/dL)	2.020±0.812	1.873±1.081	2.080±1.050	2.517±0.598	2.222±0.719	2.000±0.949
Peak direct bilirubin (mg/dL)	6.167±2.260	5.393±2.409	3.260±0.940*	3.800±0.566	3.478±1.085*	3.500±1.022**
Peak ALT (IU/L)	154.20±20.84	153.47±42.22	108.40±20.18*	80.50±70.59**	122.22±50.08	101.67±57.12**
Peak AST (IU/L)	202.20±12.32	195.53±19.85	153.80±19.99*	110.00±71.76**	163.33±49.40	149.67±61.99**,‡
Peak AP (IU/L)	597.60±216.94	331.27±173.26	313.00±221.74*	271.67±135.38	426.33±255.35	463.83±267.67‡
Peak GGT (IU/L)	131.07±37.81	109.73±45.66	95.20±57.12*	62.17±38.24**	82.78±47.31*	99.40±45.71‡

* p<0.05 vs control group <1500 g; ** p<0.05 vs control group >1500 g; † p<0.05 vs treated pediatric patients <1500g; ‡ p<0.05 vs treated pediatric patients >1500g

PN – parenteral nutrition; ALT – alanine aminotransferase; AST – aspartate aminotransferase; AP – alkaline phosphatase; GGT – gamma-glutamyl transpeptidase; BW – body weight; n – number of patients

and children [16]. Cholestasis and cholelithiasis are often observed in infants, whereas adults more often develop steatosis [16, 17]. The most common histological changes in children with cholestasis are portal fibrosis (100%), pericellular fibrosis (95%) and bile ductile proliferation (90%) [18]. Biliary cirrhosis is a late feature, which is associated with death within 6 months. Steatosis is very rare in infants, but can occur if a child receives inappropriately high parenteral carbohydrate calories, and is reversible after reduction of calories.

The earliest clinical sign is jaundice and increase of CB within 2 weeks of starting TPN with tendency to rise during episodes of intercurrent sepsis. Persistent elevation of serum bilirubin (more than 200 μmol/L) suggests an adverse prognosis [19]. Kelly [18] found an increase in AP and amino transferases within 4-6 weeks in approximately 34% of infants. As AP rise may also be secondary to rickets in this group of infants, Black et al. [20] suggested that GGT might be an early marker of TPN-associated cholestasis. We suppose that we did not find any statistical difference in GGT level between the investigated groups because of its rapid changes during the early infancy. Farrell et al. [21] suggested that the most sensitive indicator of early cholestatic liver disease would be an increase in serum bile acid concentrations, particularly sulfated lithocholate.

There was no difference in peak serum GGT (except between the control group and treated pediatric patients >1500 g BW), probably because of the physiological differences in normal values within the first weeks of life.

In a significant number of children on total parenteral nutrition, liver diseases progress to biliary cirrhosis, portal hypertension and liver failure. Lack of enteral feeding gives rise to reduced gut hormone secretion, reduction of bile flow and biliary stasis [16]. Intestinal stasis leads to bacterial overgrowth, bacterial translocation and sepsis, increasing the cholestasis and production of lithocholic acid which is toxic to the liver [18].

Neonates especially at risk are those with low birth weight and low gestational age [15, 18]. It may be related to immaturity of the neonatal liver. Contractility of gall bladder in premature infants (27-32 weeks) is impaired [22]. The total bile salt pool is also reduced. Hepatic uptake and synthesis of bile salts are diminished and enterohepatic circulation is reduced compared with full-term infants or adults. In addition, glutathione is reduced in newborn, while sulfation, an important step in solubilization of toxic bile salts, is deficient [18].

TPN-induced hepatic dysfunction is potentially reversible, but in many children, especially premature, it is impossible to discontinue TPN. That is why it is important to prevent the development of hepatic dysfunction. Introduction of some enteral nutrition, prevention of sepsis and addition of glutamine to TPN solutions seem to be important [18]. To improve bile flow and reduce the formation of biliary sludge, oral UDCA may be advantageous [8].

UDCA has a complex mechanism of activity. Chronic administration of UDCA is safe, reduces the clinical symptoms, improves the biochemical parameters, and even the histopathology picture of the affected organ [23]. However, this type of therapy usually does not lead to complete cure.

The direct effect of this hydrophilic drug during chronic administration should be attributed to the alteration of the whole pool of biliary acids involving reduction of the amount of toxic hydrophobic acids and decrease of the bile acid saturation [23]. This effect results from the absorption of exogenous UDCA, its hepatoenteric circulation, as well as from competitive inhibition of the intestinal absorption of other biliary acids. UDCA also enhances the uptake of bile acids by hepatocytes and their release into bile. It is also potent cholagogue [24] and may improve bile flow and reduce gall bladder and intestinal stasis. UDCA is a drug which reduces the passage of cholesterol from hepatocytes into the bile, decreasing biliary secretion of cholesterol and reducing its lithogenicity (prevention of

formation of gallstones) [23]. It has effect on the immune system by reducing the expression of HLA I antigens on hepatocytes, reducing the levels of cytokines (including IFN gamma, IL-2, IL-4) and inhibiting the proliferative response of lymphocytes to mitogenic stimulation [25].

The first research on the effectiveness of UDCA in liver and biliary duct pathology, reported by Makino et al. [26] 10 years ago, suggested the possibility of application of this drug in the treatment of cholesterol cholelithiasis. Administration of UDCA at doses of 15-30 mg/kg/daily in a group of few premature infants with cholestasis connected with parenteral nutrition led to the reduction of bilirubin levels after 2 weeks of treatment with no side-effects, which was also confirmed in the report by Levin et al. [7]. Since that time, numerous clinical trials concerned with the therapeutic efficacy of UDCA in liver pathology (primarily associated with cholestasis) have been carried out.

The application of UDCA in pediatric clinic took place later than in the treatment of adults because of the lack of fully formulated indications and controversy concerning the effectiveness of the therapy, as well as the concern of potential side effects [23]. The main effect of UDCA in premature infants with PNAC might be more to improve bile flow than act as a cytoprotective agent. Neonatal enterohepatic circulation is not as efficient as in the adult and is characterized by decreased bile acid secretion, synthesis and flow as well as decreased hepatic uptake of bile salts and inefficient ileal uptake [27]. Compensation for relatively inefficient uptake of portal bile salts is manifested by an increase in fasting and postprandial serum bile acid concentrations [15]. This elevation in circulating serum bile acid concentrations is at times referred to as physiological cholestasis, and during the first 6 months of life, the bile acids concentrations can approach that of adults with clinical cholestasis.

Heubi et al. [4] found tauroursodeoxycholic acid (TUDCA) ineffective in preventing the development or treatment of TPN-associated cholestasis in neonates. None of the previously published studies (except Heubi's, who used TUDCA) was designed to determine whether UDCA therapy could prevent liver disease. The data accumulated so far [23] concerning the application of UDCA in pathology of the liver and bile ducts in children point to its usefulness in numerous diseases (mainly intrahepatic cholestasis). Such therapy should be instituted in order to improve the quality of life, reduce the incidence of complications and postpone the transplantation of the liver until the time the child is older. These are the reasons why we tried to confirm that UDCA is efficient in preventing cholestasis in parenterally fed premature babies.

CONCLUSION

In our study, cholestasis was prevented or developed significantly later in treated groups than in the controls, especially in pediatric patients where the incidence of cholestasis was mostly reduced (in 6 cases). UDCA appears to be very successful in preventing or reducing the symptoms of cholestasis because all parameters of cholestasis were significantly reduced in treated groups. The difference in efficacy of UDCA treatment between lower and higher birth weight infants could not be proven. We hope that additional investigations (we started to administer UDCA to every infant on PN, beginning from the time when resorption ability was achieved) involving a larger number of treated infants will show more accurate results, which will confirm UDCA efficacy in prevention of cholestasis. Some previous and current investigation results seem to be promising.

Further studies of biliary lithogenicity and enterohepatic circulation of neonates may help to provide a better window into the prevention of neonatal cholestasis. In future, when soluble UDCA (sulphate conjugates) becomes available, it will be possible to introduce UDCA therapy immediately because it will be added directly to TPN solutions.

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Превентивни утицај урзодеоксихолне киселине на појаву холестазне болести јетре код одојчади на парентералној исхрани

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КРАТАК САДРЖАЈ

Увод Холестаза као последица парентералне исхране могућа је компликација код превремено и деце рођене у термину која су на дуготрајној парентералној исхрани.

Циљ рада Циљ рада је био да се испита утицај примене урзодеоксихолне киселине (*UDCA*) на појаву холестазе код новорођенчади на дуготрајној парентералној исхрани.

Методе рада Ова ретроспективна студија обухватила је 56 новорођенчади, која су сврстана у три групе. Контролну групу је чинило 30 деце с веома малом телесном масом на рођењу (1500 *g*), а остале групе 11 педијатријских болесника и 15 хируршких болесника лечених применом *UDCA*. Биохемијске анализе су вршене два пута недељно.

Резултати Код све новорођенчади се развила холестаза, али је време од примене парентералне исхране до појаве холестазе било статистички значајно дуже код деце која су примала *UDCA*. Просечна дужина парентералне исхране пре појаве холестазе у контролној групи болесника била је 25 дана, у групи педијатријских болесника 39 дана, а у групи хируршких болесника 34 дана. Повећање нивоа конјугованог билирубина у серуму, *AST*, *ALT* и алкалне фосфатазе било је статистички значајно мање у групама болесника који су лечени применом *UDCA*. У погледу повећања вредности ових параметара, није било статистички значајне разлике између педијатријских и хируршких болесника, нити између деце телесне масе до 1500 *g* и новорођенчади која су на рођењу била тежа од 1500 *g*. Време трајања холестазе је било статистички значајно краће код свих болесника који су лечени применом *UDCA*. Утврђена је статистички значајна разлика у времену до достизања потпуног ентералног уноса између групе педијатријских и хируршких болесника.

Закључак Холестаза се појавила знатно касније код деце која су примала *UDCA*, за разлику од контролне групе. *UDCA* је врло успешна у смањењу симптома холестазе. Нисмо, међутим, могли да докажемо разлику у ефикасности примене *UDCA* између лечене деце с телесном масом нижом и вишом од 1500 *g* на рођењу.

Кључне речи: парентерална исхрана; холестаза; новорођенче; урзодеоксихолна киселина

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