Ursodeoxycholic acid therapy for intractable total parenteral nutrition-associated cholestasis in surgical very low birth weight infants

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ABSTRACT

Introduction: Cholestasis associated with long-term total parenteral nutrition (TPN) occurs commonly in very low birth weight (VLBW) infants. Indeed, the majority of infants with TPN-associated cholestasis (TPNAC) respond very well to TPN withdrawal and full enteral feeding, yet some of them do not respond and have the potential for development of intractable cholestasis. It has been demonstrated that ursodeoxycholic acid (UDCA) has beneficial effects in treating TPNAC in various age groups. Nevertheless, the clinical data of UDCA use in VLBW infants, the most vulnerable group, are limited. We report the results of administration of UDCA therapy to VLBW infants with intractable TPNAC.

Methods: Medical records of VLBW infants who were treated with oral UDCA, at dose of 15-20 mg/kg/day, for intractable TPNAC were reviewed from 1999-2001. Treatment effectiveness was evaluated by monitoring the biochemical hepatic markers, including total bilirubin, direct bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT).

Results: A total of 13 infants were identified with the diagnosis of intractable TPNAC and they were treated with UDCA therapy. There was a significant reduction in serum levels of direct bilirubin, total bilirubin (p-value equals 0.0001) and AST (p-value equals 0.001). However, the serum levels of ALP, ALT and GGT showed a trend of improvement, yet none of them was statistically significant. Serum direct bilirubin was noted as the first marker to respond to UDCA therapy. It declined steadily during the course of therapy except in two intervals at the sixth and twelfth week of therapy that apparently associated with severe sepsis. There were no serious side effects noted.

Conclusion: Our series data suggest that UDCA is safe and may be a potential treatment for intractable TPNAC if used within two weeks after TPN withdrawal and full enteral feeding. Sepsis may alter the effectiveness of UDCA therapy.

Keywords: cholestasis, intractable cholestasis, total parenteral nutrition, ursodeoxycholic acid, very low birth weight infants

Singapore Med J 2006; 47(2):147-151

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INTRODUCTION

Total parenteral nutrition (TPN) has a major role in the modern neonatal care. Nevertheless, intrahepatic cholestasis predominantly complicates the use of long-term TPN, particularly in very low birth weight (VLBW) infants[1-3]. In the majority of cases, total parenteral nutrition-associated cholestasis (TPNAC) usually resolves later after cessation of the TPN and full enteral feeding[4-6]. However, in few patients, cholestasis does not resolve and may progress to severe hepatobiliary damage and death[7-9]. Those infants are often more sick and have a stormy hospital course with frequent episodes of sepsis[10-11], narcotising enterocolitis[7-12] and prolonged TPN course[9,13] that may intensify the TPNAC.

Several therapeutic modalities for TPNAC have been described in the medical literature, such as ursodeoxycholic acid (UDCA)[14-17]. In clinical practice, UDCA has beneficial effects in treating a wide spectrum of cholestatic liver disorders[18,19]. Improvement of TPNAC has been demonstrated following UDCA therapy in various age groups[14-16]. Nevertheless, in VLBW infants, the most susceptible group, the clinical data of UDCA use are limited[17,20]. In this retrospective study, we report the results of administration of UDCA therapy for intractable TPN-associated cholestasis in VLBW infants.

Table I. Clinical data and ursodeoxycholic acid (UDCA) therapy for 13 patients.

Patients	Sex/GA (weeks)	BW (g)	Diagnosis	Age at the onset of TPN (days)	TPN duration (days)	Age at onset of cholestasis (days)	Age at full feeding (days)	Age at the onset of UDCA (days)	UDCA duration (days)
1	M / 29	1,180	Severe NEC	3	82	30	88	105	68
2	M / 31	1,440	Multiple intestinal atresia	4	69	32	73	100	30
3	F / 27	1,010	Sepsis, severe NEC	3	70	42	75	83	16
4	F / 28	1,040	Severe NEC	3	29	34	43	57	30
5	F / 31	1,200	Oesophageal atresia	3	53	37	60	76	30
6	M / 28	1,150	Sepsis, severe NEC	2	47	33	50	57	178
7	M / 34	1,200	Severe NEC	3	67	51	73	84	74
8	F / 32	1,500	Sepsis, severe NEC	2	100	41	104	110	190
9	M / 29	1,190	Severe NEC	4	39	29	43	48	21
10	F / 33	1,500	Multiple intestinal atresia	3	56	28	59	63	59
11	F / 24	715	Severe NEC	4	102	39	109	115	103
12	F / 26	750	Sepsis, severe NEC	3	33	30	38	60	135
13	M / 29	765	Severe NEC	5	60	45	67	72	177
Mean±SEM	**29.3±1**	**113±75**		**3.2±0.3**	**62±7**	**36.2±2**	**68±6**	**79±6**	**85±17**

GA: Gestational age; BW: Birth weight; TPN: Total parenteral nutrition; NEC: Necrotising enterocolitis; UDCA: Ursodeoxycholic acid; M: Male, F: Female; SEM: Standerd error of the mean.

Table II. Values of serum bilirubin and hepatic enzymes at pre- & post-UDCA therapy.

Liver profile	Normal values	Pre-UDCA	Post-UDCA	p-value	Onset of response (weeks)
Total Bilirubin (umol/L)	<120	244 ± 38	16 ± 2	0.0001	1.5 ± 0.3
Direct Bilirubin (umol/L)	<34	202 ± 32	10 ± 2	0.0001	1.5 ± 0.3
ALP (U/L)	117-390	852 ± 67	788 ± 216	0.74	2.7 ± 0.5
ALT (U/L)	2-40	101 ± 12	80 ± 11	0.23	3.8 ± 0.8
AST (U/L)	<77	185 ± 22	80 ± 14	0.001	3.3 ± 0.9
GGT (U/L)	13-204	284 ± 57	231 ± 52	0.48	1.6 ± 0.2

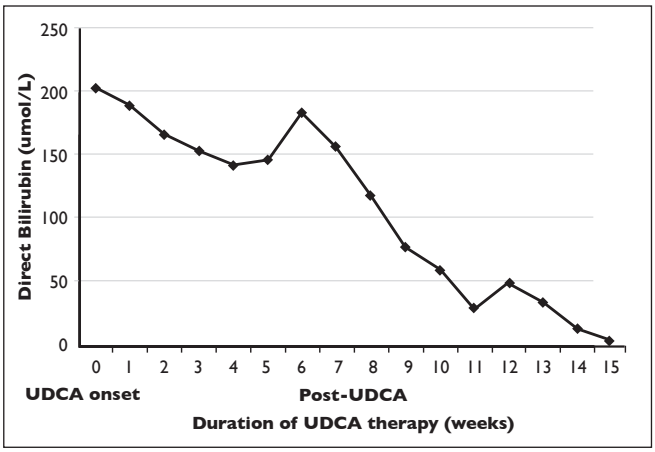
ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: ɣ-glutamyl transferase; UDCA: Ursodeoxycholic acid.

The values are expressed as Mean±SEM (standerd error of the mean).

METHODS

In our institution, VLBW infants (birth weight ≤1,500 grams), usually receive TPN that consists of lipid solution (Lipofundin MCT/LCT 20%, B Braun Medical Inc, Melsungen, Germany), an amino acid solution (Trophamine, B Braun Medical Inc, Carrollton, Texas, USA), dextrose, electrolytes, trace elements and vitamins to provide the daily nutritional needs. As soon as the infants are ready for enteral feeds, expressed breast milk (EBM) or special care formula for premature infants (Similac Special Care 24, Ross Laboratories, Columbus, OH, USA) are

Fig. 1 Serum direct bilirubin response to ursodeoxycholic acid (UDCA) therapy.



initiated and increased gradually as tolerated, while the TPN is decreased, providing the optimal nutrition which maintains appropriate daily weight gain.

The diagnosis of TPNAC was made in VLBW infants who had direct hyperbilirubinaemia (direct bilirubin >34 μmol/L) after a prolonged TPN course (>two weeks) and with a normal baseline liver profile prior to the use of TPN. However, the diagnosis of intractable TPNAC was defined in VLBW infants as a persistent direct hyperbilirubinaemia while off TPN and already on full enteral nutrition. All infants had ultrasonography of the hepatobiliary system that excluded the anatomical deformity and obstructive lesions. Serological tests for viral hepatitis and cytomegalovirus, metabolic screening for hypothyroidism and galactosaemia were unremarkable. Urinary tract infection was excluded in all infants.

During the period from July 1999 to June 2001, charts of VLBW infants who had the diagnosis of intractable TPNAC and received UDCA (Urdox®, CP/Pharma, UK) were reviewed. The UDCA (15-20 mg/kg/day) was given orally in two divided doses to those infants until the serum levels of direct bilirubin were normalised. The liver function tests (LFT) including total bilirubin, direct bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyl transferase (GGT) were performed just before, as baseline values, commencing UDCA therapy and weekly until UDCA cessation, thereafter LFT was monitored twice monthly for three months. Data were collected regarding the gestational age, birth weight, clinical diagnosis, TPN duration, onset of cholestasis, age at full enteral feeds, onset and duration of UDCA therapy.

Results were expressed as a mean ± SEM. Data was analysed by analysis of variance of the means for continuous variables, followed by least significant difference post hoc procedure to compare the mean differences between the groups. Paired t-test was used to compare means of pre- and post-therapy. Two-tailed tests were used and a p-value <0.05 was considered to be statistically significant.

RESULTS

A total of 13 infants who met the inclusion criteria of the intractable TPNAC were analysed. There were six males and seven females, with a mean gestational age of 29.3±1 weeks and a mean birth weight of 1,130±75 grams. The main clinical diagnoses, that obligating provision of TPN, were severe nercotising enterocolitis (NEC) and intestinal atresia. The TPN commenced at a mean age of 3.2±0.3 days, thereafter the cholestasis occurred at a mean age of 36.2±2 days. The TPN was required for a mean duration of 62±7 days and the full enteral nutrition was attained at a mean age of 68±6 days. The UDCA therapy was started at a mean age of 79±6 days for a mean duration of 85±17 days (Table I).

The effect of UDCA on biochemical values is demonstrated in Table II. UDCA therapy was associated with significant reduction in serum direct bilirubin, total bilirubin (p=0.0001) and AST (p=0.001) parameters. During the same period of treatment, the serum levels of ALP, ALT and GGT showed a trend of improvement, yet none of them reached statistical significance. The serum levels of direct bilirubin and GGT were the earliest markers noted to decline at a mean duration of 1.5±0.3 and 1.6±0.2 weeks, respectively following initiation of UDCA therapy. However, the serum levels of ALT was the last marker observed to respond to UDCA therapy at a mean duration of 3.8±0.8 weeks (p=0.006).

The mean serum levels of direct bilirubin were noted to decrease steadily during the course of UDCA therapy, except in two periods at the sixth and twelfth week of therapy (Fig. 1). Ultimately, the mean value approached to 33±9.6 umol/L (normal level <34 umol/L). There were no significant side effects related to UDCA apart from mild diarrhoea in three patients, and there was no evidence of recurrence of cholestasis after cessation of UDCA therapy.

DISCUSSION

Total parenteral nutrition associated cholestasis occurs frequently in VLBW infants[1-3]. The precise mechanism by which TPN causes hepatic dysfunction in infants is hidden. However, different mechanisms have been suggested such as immaturity of the enterohepatic circulation, biliary stasis and the increased production of hepatotoxic bile acids[21,22]. In fact, the majority of infants with the TPN-associated hepatobiliary injury respond very well for the conventional manoeuvres that consist of TPN withdrawal and full enteral feeding[5,6], but some of them do not recover and develop intractable cholestasis. This advanced disorder was described recently in premature infants and was related to several risk factors, such as gastrointestinal surgery for severe NEC, intestinal atresia, prolonged TPN duration and frequent episodes of sepsis[23-25]. These risk factors were similar to those in the present series.

To date, there is no universally accepted treatment for intractable TPN-associated cholestasis. UDCA is a hydrophilic bile acid that is increasingly used in the treatment of various chronic cholestatic hepatic disorders[18,19], including the TPNAC[14-17]. It is normally present in human bile at low concentration that accounts for up to 4% of the bile acid pool. It is passively absorbed in the jejunum; thereafter, it is conjugated in the liver. UDCA conjugates are absorbed mainly in the distal ileum, where they compete with endogenous bile acids for active transport and supply the enterohepatic circulation[18,19]. Experimental studies have suggested that UDCA has a role in protection of cholangiocytes against cytotoxicity of bile acids[19,26].

The results of our study revealed that UDCA therapy induced biochemical improvement in liver function tests in VLBW infants with TPN-associated cholestasis. Such observation was first noted by Lindor et al[15]. Thereafter, similar results were confirmed in adult[15,16] and paediatric population[14,17,20,27]. In our series, serum direct bilirubin responded to UDCA administration within the second week of the therapy course, however it required about four months of UDCA therapy to normalise. Perhaps, this long period of recovery could be related to the two episodes of increment of serum direct bilirubin during UDCA therapy; those two episodes were associated with severe bacterial and fungal sepsis. Indeed, severe infection has been noted to alter the UDCA efficacy in treatment of patients with cholestasis[28].

Furthermore, several therapeutic modalities have been investigated to prevent or to treat the intractable form of TPNAC. A gastrointestinal hormone, such as cholecystokinin (CCK), was found to increase the bile flow; it has been demonstrated to be beneficial in animal studies[29,30], but the result was disappointing in premature infants. Rintala et al[24] determined the effect of CCK therapy on serum direct bilirubin levels where they found that CCK initiated the decline of direct bilirubin levels, however, they utilised UDCA for four to six consecutive weeks to maintain the response. An invasive surgical intervention involving operative irrigation of biliary tree was helpful in limited number of patients[23,25].

In severe cases, onset of resolution of the persistent TPNAC is unpredictable following TPN cessation and institution of enteral feedings and if it is sustained, there is a high risk of irreversible hepatobiliary injury with liver failure and death[7,8]. Therefore, it is unclear when to initiate the therapeutic interventions. In our series, favourable outcomes were observed following institution of UDCA therapy within two weeks after TPN cessation and establishment of full enteral nutrition. Indeed, lack of control in the present study raises a debate regarding the precision of our results. The seriousness of such conditions and the concern of progress to an irreversible stage of hepatic dysfunction would preclude conducting a randomised control trial.

In conclusion, our current data suggest that UDCA is safe and may be a potential therapy for intractable TPNAC, if used within two weeks after TPN withdrawal and full enteral feeding. However, sepsis has a major influence on the natural course of TPNAC and on the effectiveness of UDCA therapy.

ACKNOWLEDGMENTS

We would like to thank Professor Youssef Al-Eissa for his support and for reviewing the article, and Dr Ahmad Saleh for his statistical assistance.

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