CLINICAL INVESTIGATION

Parenteral Nutrition-Associated Liver Disease: a Retrospective Study of Ursodeoxycholic Acid Use in Neonates

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OBJECTIVES: To verify the effect of ursodeoxycholic acid (UDCA) on the duration of neonatal parenteral nutrition-associated liver disease.

METHODS: Retrospective cohort study of neonates in intensive care between 2004 and 2007 presenting with parenteral nutrition-associated liver disease.

RESULTS: Of 118 eligible infants, 64 received UDCA. Cholestasis lasted longer in the UDCA group (79 vs. 50 days, $p=0.001$). However, treatment was delayed for a median of 24 days after cholestasis onset. Multivariate Cox regression analysis showed no association between UDCA and cholestasis duration. The rate of decline of conjugated bilirubin was greater in treated patients (median 0.084 mg/dL/day vs. 0.60 mg/dL/day; $p=0.009$) and weight gain was greater (22.8 vs. 17.7 g/kg/day, $p=0.010$).

CONCLUSIONS: UDCA therapy was not associated with the duration of parenteral nutrition-associated liver disease. A delay in treatment initiation might explain this result. UDCA therapy was associated with a faster decline of conjugated bilirubin and greater weight gain.

INDEX TERMS: hyperbilirubinemia, infant, liver disease, neonate, parenteral nutrition, premature, ursodeoxycholic acid

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INTRODUCTION

Parenteral nutrition (PN) is used in neonatal intensive care in newborns whose nutritional needs cannot be entirely met by enteral feeding. A known complication, however, is PN-associated liver disease (PNALD).¹ Major risk factors for PNALD include prematurity, low birthweight, early and prolonged exposure to PN, sepsis, and insufficient use of the gastrointestinal tract.^{2–4} While PNALD ordinarily resolves with complete enteral feeding, it can progress to cirrhosis, hepatic failure, and death if prolonged.¹

Ursodeoxycholic acid (UDCA), also known as ursodiol, is a choleretic agent with cytoprotective effects on hepatocytes and cholangiocytes.^{5,6} This medication has been successfully used for treating PNALD in children and adults.^{7–12} In neonates, the studies conducted so far have varied in

methodology and have evaluated UDCA therapy either in prevention or treatment of PNALD.^{13–20} These studies have yielded conflicting results, some suggesting a reduction in hepatic markers or PNALD duration, whereas others did not observe such effects.

We performed a retrospective cohort study with the primary objective of comparing time to resolution of PNALD in neonates receiving UDCA to that in a control group not receiving UDCA. Secondary outcomes included a comparison of weight gain and peak values of hepatic markers. The incidence of necrotizing enterocolitis (NEC) during the course of cholestasis was used as a safety indicator.

SUBJECTS AND METHODS

Patients hospitalized in a neonatal intensive care unit between 2004 and 2007 were identi-

fied on the basis of their laboratory records. All patients with 2 or more consecutive serum-conjugated bilirubin concentrations of ≥ 2 mg/dL were included. Patients who did not receive PN at the time of cholestasis onset or those with cholestasis caused by a factor other than PN were excluded. Patients with positive blood cultures within 7 days of cholestasis onset were excluded to rule out sepsis as a cholestasis trigger.²

Treatment

UDCA therapy consisted of a suspension of 60 mg/mL (osmolality 3983 mOsm/kg) prepared by the pharmacy department from commercially available tablets.²¹ Dosage, initiation of therapy, and duration were left to the discretion of the treating physician and team. Patients not receiving UDCA were included in the control group. Pharmacy records for included patients were reviewed for the use of medications listing cholestasis or hyperbilirubinemia as a side effect (cloxacillin, fluconazole, ibuprofen, indomethacin, phenytoin, trimethoprim/sulfamethoxazole).²² Enteral feeding progression was also noted.

Outcome Measures

Resolution of cholestasis was defined as the time at which conjugated bilirubin decreased below 2 mg/dL. Time to cholestasis resolution was the main outcome. Follow-up ended at hospital discharge or death. Weight gain (g/kg/day) was defined as the differences between weight at onset and weight at the end of cholestasis divided by the weight at the onset of cholestasis and its duration.

Peak levels of liver function tests during cholestasis and minimum albumin levels were compared, as was the rate of decline in conjugated bilirubin from its peak.

NEC is an adverse event that could be related to the administration of hyperosmolar oral solutions in preterm infants.²³ We therefore noted the presence of NEC as well as the timing of NEC as compared to UDCA therapy.

An additional analysis was performed that included only those patients in whom UDCA was started within 14 days of cholestasis onset, in order to control for the effects of a delay between cholestasis onset and the initiation of UDCA therapy, as detected during the analysis of our results.

Figure. Patients assigned to intervention and control groups. UDCA, ursodeoxycholic acid.

Statistical Analysis

Categorical variables were compared using Fisher's exact test. For dichotomous variables, the chi-square test was used. Normally distributed continuous variables are presented as means $\pm$ SD and were compared using the Student *t*-test. For data not normally distributed, they are presented as median (interquartile range) and were compared with the Mann-Whitney *U* test.

Multivariate Cox regression analyses were performed with potential confounders with uneven distribution between groups, wherever the *p* value was <0.15 on univariate regression. Multivariate linear regression analyses were performed with secondary outcomes according to the same criteria. All statistical analyses were done using SPSS version 15.0 software (SPSS Inc, Chicago, IL).

Ethical Considerations

The protocol was approved by the Research Ethics Committee and the Director of Medical and Academic Affairs of Sainte Justine Hospital (CHU Sainte-Justine).

RESULTS

Of 145 patients identified from laboratory reports, 118 were included in the study (Figure). Among the 27 excluded patients, 9 did not receive PN; 10 had positive blood cultures within 7 days of cholestasis onset; and 8 had an identified cause

Table 1. Patient Characteristics

Characteristic	Ursodeoxycholic Acid Group (n = 64)	Control Group (n = 54)	p Value
No. of births at Sainte Justine Hospital (%)	56 (87.5)	43 (79.6)	0.317
No. of males (%)	38 (59.3)	36 (66.7)	0.450
Median weeks of gestational age (interquartile range)	27.1 (26.0-30.9)	30.8 (27.0-36.0)	0.006
Median birthweight (g) (interquartile range)	923 (770-1440)	1290 (870-2828)	0.010
No. with perinatal asphyxia (%)	3 (4.7)	4 (7.4)	0.701
No. with gastroschisis (%)	4 (6.2)	1 (1.6)	0.373
No. with omphalocele (%)	0 (0)	2 (3.7)	0.207
No. with intestinal atresia (%)	1 (1.6)	4 (7.4)	0.177
No. with intestinal malrotation (%)	2 (3.1)	4 (7.4)	0.410
Median 1-min APGAR score (interquartile range)	6 (4-8)	5 (2-7)	0.156
Median 5-min APGAR score (interquartile range)	7 (6-9)	7 (6-8)	0.475
Median 10-min APGAR score (interquartile range)	8 (7-9)	8 (7- 9)	0.899
No. with intrauterine growth restrictions (%)	16 (25)	15 (27.8)	0.834
No. of positive blood cultures prior to cholestasis (%)	4 (6.2)	0 (0)	0.124

APGAR, appearance, pulse, grimace, activity, respiration.

for cholestasis: biliary atresia (1 patient), neonatal sclerosing cholangitis (1 patient), inspissated bile syndrome (3 patients), galactosemia (1 patient), congenital hypothyroidism (1 patient), and congenital rubella (1 patient). Among included patients, 64 received UDCA; the 54 who did not receive UDCA were assigned to the control group. The 2 groups were similar except for median gestational age and birthweight, which were significantly lower in the UDCA group (median 27 vs. 31 weeks, $p=0.006$; and 923 vs. 1290 g, $p=0.01$, respectively) (Table 1). Seven patients died during follow-up. Causes of death included NEC (2 patients), intraventricular hemorrhage (1 patient), multiorgan failure (1 patient), septic shock (2 patients), and bronchopulmonary dysplasia (1 patient). None of these deaths was directly attributed to cholestasis, and none of the NEC deaths occurred in the UDCA group.

The median (interquartile range) UDCA dose used in the study period was 24.9 mg/kg/day (20.0, 29.4). Time from diagnosis of cholestasis to initiation of UDCA therapy was 24 (12, 37) days. Treatment lasted 35 (22, 64) days. Time to cholestasis resolution following the start of UDCA was 39 (25, 68) days.

Although the median ages at onset of enteral feeding were comparable between groups (8 [3, 15] days for the intervention group vs. 7 [4, 13]

days for the control group; $p=0.719$), the age at which it reached 120 mL/kg/day and the total duration of PN were significantly higher in the UDCA group (40 [30, 52] days vs. 31 [21, 40] days, respectively, $p=0.002$; and 42 [31, 60] vs. 33 [18-50] days, $p=0.007$, respectively). Interruptions in enteral feeding were similar in both groups (1 [0, 3] day vs. 1 [0, 3] day, respectively, $p=0.380$).

The numbers of patients receiving medications with cholestasis as a side effect were not significantly different between groups (50 [78.1%] in the treatment group vs. 35 [64.8%] in controls, $p=0.149$), nor were the numbers of patients with positive blood cultures at 7 or more days after cholestasis onset (7 [10.9%] vs. 4 [7.4%], respectively, $p=0.546$).

Primary Outcome

Cholestasis took significantly longer to resolve in the UDCA group (median 79.0 days vs. 50.0 days, respectively; $p=0.001$). On univariate Cox regression, variables associated with cholestasis duration were birthweight ($p=0.003$), gestational age ($p=0.04$), medications with cholestasis as a side effect ($p=0.028$), peak conjugated bilirubin levels ($p<0.001$), duration of PN ($p<0.001$), age at which enteral feedings reached 120 mL/kg/day ($p=0.001$), presence of positive blood cultures before cholestasis onset ($p=0.116$), and UDCA

Table 2. Multivariate Cox Regression Analysis

Variable	Unadjusted Regression Coefficient β	Adjusted Regression Coefficient β	Hazard Ratio (95% CI)	Adjusted p Value
Birthweight (kg)	0.488	0.829	2.29 (1.03-5.10)	0.043
Gestational age (wk)	0.071	-0.057	0.945 (0.811-1.10)	0.464
Peak conjugated bilirubin level (mg/dL)	-0.015	-0.010	0.058 (0.057-0.058)	0.009
Treatment with medications listing cholestasis as a side effect	-0.693	0.182	1.20 (0.543-2.65)	0.652
Age at which enteral feedings reached 120 mL/kg/day (days)	-0.023	-0.011	0.989 (0.969-1.01)	0.275
Duration of parenteral nutrition (days)	-0.021	-0.018	0.983 (0.966-0.99)	0.038
Cholestasis onset preceded by positive blood cultures	-1.593	0.028	1.028 (0.131-8.08)	0.979
Ursodeoxycholic acid	-1.067	-0.512	0.599 (0.321-1.12)	0.107

CI, confidence interval

therapy ($p < 0.001$). Duration of PN was the only variable that did not fit the assumptions of the Cox model (proportional hazards). This variable was therefore transformed into a time-dependent one (cumulative number of days receiving PN), which remained significant on univariate analysis ($p < 0.001$). On multivariate Cox regression analysis, only birthweight, peak conjugated bilirubin level, and cumulative number of days receiving PN remained significantly associated with cholestasis duration (Table 2).

Secondary Outcomes

Secondary outcomes differed significantly between groups for peak conjugated bilirubin, peak alkaline phosphatase (ALP), and weight gain (Table 3). The incidence of NEC after cholestasis onset (safety indicator) was similar between groups (Table 3). None of the observed NEC cases occurred after UDCA therapy onset.

Factors associated with weight gain on univariate linear regression were birthweight ($\beta = -2.95$; $p = 0.008$), gestational age ($\beta = -0.531$; $p = 0.012$), and UDCA therapy ($\beta = 5.19$; $p = 0.01$). On multivariate regression, UDCA remained the only factor of significance (adjusted $\beta = 4.32$; $p = 0.032$).

Hospital stay was longer in the treated group (median, 101 days [78, 125] vs. 58 [33, 99], respectively, $p < 0.001$), but there were fewer deaths (1 [1.6%] vs. 6 [11.1%], respectively, $p = 0.046$).

Additional Analyses

For the 19 patients in whom UDCA was ad-

ministered within 14 days of cholestasis onset (herein called the UDCA-14 group), there were no significant differences in cholestasis duration (median 61.0 days in the UDCA-14 group vs. 50.0 days in the control group; $p = 0.315$). Birthweights were not statistically different between the UDCA-14 and control groups (median 1045 g for the UDCA-14 group vs. 1214 g for the control group; $p = 0.773$), nor was gestational age (median 30.0 weeks vs. 30.4 weeks, respectively, $p = 0.752$) or duration of PN (median 41.0 days vs. 32.0 days, respectively; $p = 0.354$). However, conjugated bilirubin levels peaked higher in the UDCA-14 group than in controls (median 5.03 mg/dL [3.04, 6.43] vs. 3.16 [2.40, 4.03], respectively; $p = 0.004$).

In the entire cohort, the rate of decline of conjugated bilirubin from its peak to resolution of cholestasis was greater in the UDCA group than in controls (median 0.084 mg/dL/day vs. 0.060 mg/dL/day, respectively; $p = 0.009$). On univariate analysis, birth weight ($p = 0.041$) and UDCA ($p = 0.049$) were significantly associated with this parameter. On multivariate regression, both of the associations remained significant (birth weight $\beta = 0.365$; $p = 0.041$; UDCA $\beta = 0.769$; $p = 0.018$).

DISCUSSION

The primary objective of our study was to determine whether the administration of UDCA would reduce the duration of PNALD. One retrospective study conducted with very-low-

Table 3. Secondary Outcomes: Liver Function Tests, Weight Gain, and Necrotizing Enterocolitis

Outcome	Ursodeoxycholic Acid Group (n=64)	Control Group (n=54)	p Value
Peak conjugated bilirubin (mg/dL)*	4.79 (3.45-7.19)	3.27 (2.57-4.50)	<0.001
Peak AST (IU/L)*	132 (85-216)	95 (54-205)	0.157
Peak ALT (IU/L)*	78 (46-135)	59 (30-155)	0.168
Peak GGT (IU/L)*	173 (113-274)	167 (95-242)	0.743
Peak ALP (IU/L)*	603 (419-751)	434 (234-566)	0.001
Minimum albumin (g/L)*	18 (15-20)	18 (16-23)	0.149
Weight gain (g/kg/day)†	22.8 ± 8.59	17.7 ± 9.95	0.010
No. of necrotizing enterocolitis cases (%)	3 (4.7)	5 (9.3)	0.467

ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase

*Median (interquartile range)

†Mean ± standard deviation

birthweight infants with PNALD showed a shorter duration of cholestasis in a group of 12 infants treated with UDCA than 18 infants in the untreated control group.¹⁶ In our retrospective cohort, patients who had received UDCA were of lower weight and gestational age at birth than the control group. They also progressed more slowly to complete enteral feeding and received PN for a longer time, which would be expected given their greater prematurity. These differences are likely to account for the longer cholestasis duration in the treated group.

After controlling for these confounders in a multivariate Cox regression, UDCA was not associated with cholestasis duration. It may, however, have positively influenced the rate of decline of conjugated bilirubin, as described in another study, which however, is only available in abstract form.²⁴ The UDCA dose was comparable to that reported in previous studies, generally between 10 and 30 mg/kg/day.^{13-17,19}

According to multivariate analysis, parameters associated with cholestasis duration were birthweight and duration of PN, which have been previously associated with PNALD.²⁻⁴

When Arslanoglu et al.¹⁹ randomized 29 preterm infants (in whom biliary salts were deficient) to evaluate the use of UDCA in facilitating the absorption of lipids, they observed a non-significant decrease in fecal fat excretion compared to that in placebo. In our study, weight gain was superior in the intervention group, even after controlling for lower birthweight and gestational age in this group. As lipids play an important role in metabolism and are a major source of energy, this

observation merits further investigation.

Three case series (26 patients) reported a reduction in cholestasis markers, such as conjugated bilirubin, in UDCA-treated newborns with PNALD.¹³⁻¹⁵ A double-blind randomized controlled pilot study of the prevention of PNALD in infants showed a reduction in gamma-glutamyl transferase (GGT) levels in a group of 15 neonates treated with UDCA compared to an increase in the 14-patient control group.¹⁹ More recently, a Turkish study showed that in 24 preterm infants receiving UDCA for prevention of PNALD, GGT was significantly lower after treatment as compared with 24 infants receiving erythromycin or 23 receiving a placebo.²⁰ In contrast, one open-label trial of tauroursodeoxycholic acid therapy for the prevention of PNALD failed to show an improvement in conjugated bilirubin, alanine aminotransferase (ALT), ALP, or serum bile acids in 22 infants compared with 30 who did not receive this medication.¹⁸ An Italian retrospective study reported that UDCA administered to 19 of 27 neonates with cholestasis had no significant effect on total and conjugated bilirubin levels and transaminases.¹⁷ In our study, peak conjugated bilirubin, an indicator of cholestasis severity, was associated with cholestasis duration.^{1,2,5,25} As this peak occurred before initiation of treatment in more than half of our patients (data not shown), we did not consider it as an outcome measure as initially planned in our protocol, but rather as a potential confounder, because it is very unlikely to have been affected by the treatment. The peaks of other hepatic parameters were not significantly different between groups, except for ALP,

which is also associated with bone metabolism. The delay in initiating UDCA after the onset of cholestasis may have contributed to this result.

With the exception of 3 cases of UDCA-associated mild diarrhea, the literature indicates that infants seem to tolerate UDCA fairly well.¹³ In our cohort, no new cases of NEC were observed following UDCA therapy onset. Although an increased risk cannot be excluded, the probability of NEC incidence appears very low and unlikely to impact significantly on whether or not to administer UDCA to a preterm infant capable of taking oral medications.

This cohort is the largest to date in the study of UDCA for treating neonatal PNALD. All eligible patients over a 4-year period were included. Although included patients were preterm and of low birthweight and had a difficult transition to full enteral feeding, the data are representative of a tertiary center population.

One limitation of our study was the delay in UDCA administration following onset of cholestasis. Although we cannot surmise the effect of earlier administration, we did conduct an additional analysis of only those patients who had received the medication within 14 days of cholestasis onset. In the 19 patients comprising this new group, UDCA was not associated with the duration of cholestasis. However, the sample size was probably too small to detect differences with sufficient power.

A second major limitation is the baseline difference between groups. It is possible that UDCA treatment was preferentially given to smaller, more premature infants. As stated before, this difference is likely to account for the longer duration of cholestasis in the treated group. A multivariate Cox regression was performed to separate the effect of UDCA from the baseline differences, but it is possible that this statistical technique could not completely isolate the effect of the medication. Still, the results we obtained should be interpreted with caution. It appears unlikely that UDCA would be detrimental to the duration of cholestasis to such an extent in this population.

In conclusion, our results showed that UDCA treatment was not associated with the duration of PNALD when introduced late after onset of the disease. However, UDCA administration may have exerted a positive effect on the rate of

decline of conjugated bilirubin and weight gain. There was no association between the use of a high osmolarity UDCA solution and the risk of NEC. Risk factors associated with prolonged cholestasis included low birthweight, high peak conjugated bilirubin values, and prolonged PN. A randomized controlled trial initiating UDCA soon after cholestasis diagnosis would help to better define the role of UDCA in the treatment of PNALD in neonates.

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Abbreviations ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; NEC, necrotizing enterocolitis; PN, parenteral nutrition; PNALD, parenteral nutrition-associated liver disease; UDCA, ursodeoxycholic acid

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