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Antenatal maternal administration of phenobarbital for the prevention of exchange transfusion in neonates with hemolytic disease of the fetus and newborn

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Objective: Hemolytic disease of the fetus and newborn infant (HDFN) can be associated with bilirubin encephalopathy, which is usually averted through neonatal exchange transfusions (EXT). However, EXT can be associated with significant procedure-related morbidity. We hypothesized that maternal oral administration of phenobarbital (PB) to women with HDFN would reduce the rate of EXT.

Study design: Cases of HDFN from January 1985 to June 2003 were reviewed. All patients who underwent serial intrauterine transfusions (IUTs) for red cell alloimmunization were included. Patients were offered oral phenobarbital (30 mg 3 times a day) after their last IUT in an effort to enhance fetal hepatic maturity. Variables studied included gestational age and hemoglobin multiples of the median at first transfusion and delivery, peak neonatal bilirubin, need for exchange transfusion, and maternal PB administration. Multivariate regression analysis was applied to determine relative risks and 95% CIs.

Results: Seventy-one patients met study criteria; 29% of the neonates underwent EXT. The use of antenatal PB was associated with a decreased incidence of EXT, 9% versus 52% ($P < .01$). After controlling for confounding variables, the relative risk for EXT after antenatal PB administration was 0.23 (95% CI: 0.06-0.76).

Conclusion: Maternal administration of PB reduces the need for neonatal EXTs in HDFN.

Hemolytic disease of the fetus and newborn infant (HDFN) can lead to significant perinatal morbidity, including encephalopathy secondary to hyperbilirubinemia. Bilirubin is liberated from the heme molecule as a result of immune-mediated hemolysis. It is transported to the hepatocyte via albumin where it then undergoes glucoronidation by a family of enzymes known as uridine-diphospho-glucuronosyltransferases (UGT). In humans, the major enzyme in this pathway is bilirubin-UDP-glucuronosyltransferase (UGT1A1). After conjugation, the bilirubin diglucuronide, which is highly water soluble, is then actively excreted into bile and

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eliminated by way of the urinary and gastrointestinal tracts. The rate-limiting step in this process is the concentration of UGT1A1.[1]

Phenobarbital (PB) has been shown to enhance the capability of the neonatal liver to conjugate and eliminate bilirubin. Studies by Brown and Zeulzer[2] and Gartner and Arias[3] in guinea pigs, and by Catz and Yaffe[4] in mice provide evidence that PB given to pregnant animals can stimulate the induction of the glucuronyl transferase enzymatic pathway in their offspring. The first human studies by Trolle[5] indicated a similar reduction in neonatal jaundice in humans from 22% to 5%. PB has been shown to increase the expression of the UGT1A1, a mechanism that has only recently been elucidated. Sugatani et al[6] discovered a 290 base pair (bp) enhancer sequence on the gene for UGT1A1 that binds PB, leading to increased production of the enzyme.

After birth, some infants affected by HDFN are unable to manage the increased production of bilirubin, leading to unconjugated hyperbilirubinemia. If untreated, this can lead to kernicterus with long-term neurologic consequences and even death. Phototherapy is usually the first line of treatment. However, if unsuccessful, neonates must undergo an exchange transfusion (EXT) to reduce the bilirubin load and the concentration of the maternal anti-red cell antibody. In a recent study, the incidence of major morbidities caused by this procedure, including transfusion reactions, line sepsis, and death after EXT, was 5%.[7] Therefore, a reduction in the need for EXTs would further improve neonatal outcomes for HDFN.

We hypothesized that maternal administration of PB before delivery in women with red cell alloimmunization undergoing serial intrauterine transfusions (IUTs) before delivery would induce neonatal hepatic maturity and reduce the need for EXT.

Material and methods

Study design

This was a retrospective case-control study of all women from January 1985 to June 2003 with documented HDFN undergoing cordocentesis and IUTs at the University of North Carolina School of Medicine in Chapel Hill, NC, and the Baylor College of Medicine in Houston, Texas. Before initiating this study, we obtained consent from the University of North Carolina institutional review board to review the medical records of the patients and neonates of interest. Cases were identified through a computerized database maintained by 1 of the authors (K.M.). All women included in this sample had either the presence of an anti-red cell antibody associated with HDFN that titered above the critical threshold or a history of a previous pregnancy affected by HDFN.

Table I Maternal and fetal characteristics

Variable	
Maternal age (y)	29.1 ± 5.1
Gravidity*	4 (1-8)
Number of IUTs*	3 (1-6)
Gestational age at first IUT (wks)	25.9 ± 3.4
Gestational age at delivery (wks)	34.4 ± 4.2
Hemoglobin at first IUT (MoMs)	0.58 ± 0.24
Hemoglobin at delivery (MoMs)	0.97 ± 0.26
Hydrops at first IUT	41%
Antibody type	(N, %)
D	49 (69)
Kell	7 (10)
D, C	10 (14)
D, C, E	2 (3)
D, C, M	1 (1)
D, E	1 (1)
c	1 (1)

All parameters expressed as means ± SD unless otherwise indicated.
* Expressed as median and range.

Pregnancies at risk for HDFN were followed intensively with surveillance for the development of fetal anemia. Before the year 2000, patients underwent serial amniocenteses for determination of their ΔOD450, using graphs created by Liley et al[8] to determine the severity of anemia. After 2000, patients were monitored with serial middle cerebral artery (MCA) peak systolic velocities (PSV) measured weekly.[9] In the first affected pregnancy, weekly MCA PSV measurements were initiated when a critical titer for the putative anti-red cell antibody was detected; in previously affected pregnancies, the MCA PSV was measured starting at 18 weeks' gestation. Fetuses with an MCA PSV greater than 1.5 multiples of the median (MoMs) underwent cordocentesis with combined intravascular and intraperitoneal transfusion if necessary. After documentation of subsequent bone marrow suppression through fetal cell stains at the time of IUT, the interval of transfusion was lengthened to 3 weeks. IUTs were repeated serially until the 35th week of gestation. After the last IUT, the patient was offered PB, 30 mg orally 3 times a day for 10 days. Delivery was planned after the treatment period. The neonate was monitored intensively in the nursery for signs of anemia and hyperbilirubinemia. Standard institutional-specific protocols that were based on the current guidelines at the time were used to determine when to initiate phototherapy or EXT.[10-12]

Medical records were extracted for the following parameters: estimated gestational age at the time of first IUT, fetal hematocrit at first IUT, total number of IUTs, gestational age at delivery, birth weight at delivery, Apgar scores, maternal PB use, levels of cord hematocrit and percentage of fetal cells at delivery, peak neonatal total and direct bilirubin, neonatal need for