

THE EFFECT OF ANTENATAL PHENOBARBITAL THERAPY ON NEONATAL INTRACRANIAL HEMORRHAGE IN PRETERM INFANTS

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ABSTRACT

Background The administration of phenobarbital to pregnant women before delivery has been thought to decrease the frequency of intracranial hemorrhage in preterm infants. To evaluate this potential neuroprotective therapy further, we determined the effect of antenatal administration of phenobarbital on the frequency of neonatal intracranial hemorrhage and early death.

Methods We studied 610 women who were 24 to 33 weeks pregnant and who were expected to deliver their infants within 24 hours. The women were randomly assigned to receive either phenobarbital (10 mg per kilogram of body weight) or placebo intravenously, followed by maintenance doses until delivery or 34 weeks of gestation. The infants born to these women underwent cranial ultrasonography to detect the presence of intracranial hemorrhage.

Results There were 309 women in the phenobarbital group and 301 in the placebo group. A total of 247 women (80 percent) in the phenobarbital group and 235 (78 percent) in the placebo group delivered within 24 hours after infusion of the study drug or administration of the last maintenance dose. Intracranial hemorrhage or early death occurred in 83 of the 344 infants born to the women in the phenobarbital group (24 percent) and in 74 of the 324 born to the women in the placebo group (23 percent; risk ratio for the infants in the phenobarbital group, 1.1; 95 percent confidence interval, 0.8 to 1.4). Among infants born before 34 weeks' gestation in whom ultrasonographic studies were performed, intracranial hemorrhage was diagnosed in 70 of 311 infants in the phenobarbital group (23 percent) and 64 of 279 in the placebo group (23 percent; risk ratio, 1.0; 95 percent confidence interval, 0.8 to 1.4).

Conclusions Antenatal administration of phenobarbital does not decrease the risk of intracranial hemorrhage or early death in preterm infants. (N Engl J Med 1997;337:466-71.)

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THERAPEUTIC interventions to prevent periventricular, intraventricular, and cerebral hemorrhages in preterm infants include the administration of drugs such as phenobarbital or indomethacin either before birth or immediately after delivery. Postnatal treatment can reduce the frequency and severity of these hem-

orrhages,^{1,2} but up to 50 percent occur before postnatal therapy can be initiated.²⁻⁴ Furthermore, events associated with premature delivery, including labor and neonatal resuscitation, may play a part in the pathogenesis of intracranial hemorrhage. For these reasons, antenatal therapy should be a more effective preventive strategy than postnatal therapy. Because of the sedative effect of phenobarbital, antenatal administration may attenuate fluctuations in neonatal blood pressure, thus lowering the risk of intracranial hemorrhage. Several studies and a recent meta-analysis have suggested that antenatal administration of phenobarbital decreases the frequency and severity of intracranial hemorrhage.^{1,5-9}

We conducted a multicenter, randomized, placebo-controlled trial of phenobarbital in women in the 24th to 33rd week of pregnancy who were expected to deliver their infants within 24 hours. The purpose of the trial was to determine the effect of antenatal phenobarbital therapy on the frequency of neonatal intracranial hemorrhage and early death.

METHODS

Study Group

Pregnant women admitted to the 10 centers participating in the National Institute of Child Health and Human Development Neonatal Research Network during center-specific recruitment hours were eligible for the study. Additional criteria for eligibility were a gestation of at least 24 weeks and less than 33 weeks according to the best obstetrical estimate, with or without labor, and an anticipated delivery within 24 hours. The criteria for exclusion from the study were an anticipated delivery within two hours, multiple congenital or chromosomal abnormalities in the fetus, a multiple gestation with more than two fetuses, administration of phenobarbital during the pregnancy, administration of indomethacin within one week before admission, and a maternal platelet count of less than 100,000 per cubic millimeter. The study

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was approved by the institutional review board of each center, and informed consent was obtained from all the women.

Administration of the Study Drug

At each center, eligible women were randomly assigned by a pharmacist to receive phenobarbital or placebo.¹⁰ The women in the phenobarbital group received 10 mg of phenobarbital per kilogram of body weight intravenously over a period of 20 to 40 minutes (maximal dose, 1000 mg), and those in the placebo group received an infusion of normal saline. The women who did not deliver within 24 hours received 100 mg of phenobarbital (or placebo) orally every 24 hours until delivery, discharge, or continuation of the pregnancy beyond the 33rd week. If a woman was readmitted before 33 weeks' gestation, the pharmacist at the study center adjusted the dose of phenobarbital (or placebo) according to the interval since the last dose.¹¹ Adverse events in the mother, such as cardiorespiratory changes and sedation, were monitored after the infusion of the study drug. Thirty minutes after the infusion, a research nurse documented the level of sedation (alert, moderately sedated, very sedated, or asleep). At two centers, the investigators were required by the institutional review board to obtain maternal and cord-blood samples for measurements of serum phenobarbital.

Evaluation of Infants

The clinical course of all infants was recorded until discharge from the neonatal intensive care unit, the 120th day of hospitalization, or death. For most infants, physical growth and neurodevelopmental outcome were assessed at 18 to 22 months of corrected age (defined as the age the child would have been if born at term).

Cranial ultrasonography was performed between 3 and 5 days, 7 and 14 days, and 36 and 42 weeks of postconceptional age or at discharge in all infants with a gestational age of less than 34 weeks. All cranial sonograms were interpreted by three radiologists not affiliated with the participating centers. At least two of the radiologists read each infant's films independently and assigned a grade for intracranial hemorrhage as follows: 0, no hemorrhage; I, hemorrhage limited to the periventricular area; II, intraventricular hemorrhage without ventricular dilatation; III, intraventricular hemorrhage with ventricular dilatation; or IV, parenchymal hemorrhage.¹² If the independent readings differed, the three radiologists reviewed the films together and reached agreement on the grade. Periventricular leukomalacia was defined as the presence of lucencies in the periventricular white matter, and post-hemorrhagic ventriculomegaly as persistent dilatation of the ventricular system.

Study Outcomes

The primary outcome was the incidence of intracranial hemorrhage during the neonatal period or death within 72 hours after birth. Secondary outcomes included intracranial hemorrhage (grade I, II, III, or IV), periventricular leukomalacia, and the neurodevelopmental outcome of infants at 18 to 22 months of corrected age.

Statistical Analysis

The results were analyzed according to the intention-to-treat method. The clinical characteristics of the mothers and infants in the two groups were compared by chi-square analyses, Fisher's exact test, t-tests, and Wilcoxon rank-sum tests. Treatment effects were estimated on the basis of relative risks and 95 percent confidence intervals.

An independent Data Safety and Monitoring Committee convened by the National Institute of Child Health and Human Development monitored the trial for efficacy, using the Lan-DeMets procedure.¹³ In addition, the trial was monitored by the method of stochastic curtailment,¹⁴ allowing a reestimation of the power to detect a benefit on the basis of the observed primary outcome.

RESULTS

From February 1993 until February 1995, when the trial was closed (see below), 5674 women were screened, of whom 1087 (19 percent) were eligible for enrollment. The reasons for ineligibility are shown in Table 1. A total of 610 of the eligible women (56 percent) were enrolled in the trial; 309 were randomly assigned to the phenobarbital group, and 301 to the placebo group.

In February 1995, with an enrollment of 610 women (planned enrollment, 1038), the Data Safety and Monitoring Committee recommended closure of the trial. This recommendation was based on an estimated relative risk of 1.0 for intracranial hemorrhage in the phenobarbital group as compared with the placebo group and a low probability of ultimately detecting a statistically significant difference between the two groups.

Characteristics of the Mothers

The base-line characteristics of the mothers in the two groups were similar (Table 2). The overall proportion of women receiving antenatal corticosteroids during the study period increased from 38 percent in the first six months to 81 percent in the last six months. However, the overall frequency of antenatal administration of corticosteroids was similar in the two groups, with 42 percent of the mothers in the phenobarbital group and 41 percent of those in the placebo group receiving a complete course (two doses of betamethasone). The fetal presentation and

TABLE 1. REASONS FOR EXCLUSION FROM THE STUDY.

REASON FOR EXCLUSION	NO. OF WOMEN (%)
Ineligible*	4587
No labor or indications for delivery	3559 (78)
Delivery imminent (within 2 hr)	444 (10)
Gestation <24 or >33 wk	307 (7)
Indomethacin therapy within previous week	246 (5)
Congenital abnormalities in the fetus	152 (3)
Enrollment in other studies	136 (3)
Phenobarbital therapy during pregnancy	63 (1)
Platelet count <100,000/mm ³	63 (1)
More than two fetuses	47 (1)
Eligible but not enrolled	477
Consent refused	229 (48)
Consent not requested	173 (36)
Physician's consent refused	59 (12)
Other reasons†	16 (3)
Total	
Screened	5674
Eligible	1087 (19)
Enrolled	610 (56)

*Some women were ineligible for more than one reason.

†Thirteen women were initially considered to be eligible but subsequently found to be ineligible, fetal death occurred in two, and one withdrew consent.

TABLE 2. CHARACTERISTICS OF THE PREGNANT WOMEN.*

CHARACTERISTIC	PHENOBARBITAL	PLACEBO	P VALUE
	GROUP (N=309)	GROUP (N=301)	
Week of gestation at enrollment	29±2	29±2	0.49
Maternal age (yr)	25±6	25±6	0.78
	no. of women (%)		
Nulliparous	141 (46)	132 (44)	0.66
Race or ethnic group			0.09
Black	136 (44)	109 (36)	
White	144 (47)	152 (50)	
Hispanic	26 (8)	32 (11)	
Other	3 (1)	8 (3)	
Education >12 yr	95 (31)	78 (26)	0.21
Married	130 (42)	137 (46)	0.39
Multiple gestation (twins)	35 (11)	23 (8)	0.12
Prenatal care†	294 (95)	289 (96)	0.60
Antepartum hemorrhage‡	31 (10)	28 (9)	0.76
Hypertension	53 (17)	49 (16)	0.77
Active labor§	170 (55)	171 (57)	0.66
Ruptured membranes	159 (51)	158 (52)	0.80
Medications			
Magnesium	128 (41)	132 (44)	0.54
Terbutaline	95 (31)	102 (34)	0.41
Antibiotics	169 (55)	167 (55)	0.84
Corticosteroids	183 (59)	176 (58)	0.85
Vaginal delivery	198 (64)	195 (65)	0.83

*Plus-minus values are means ±SD.

†Prenatal care was defined as at least one prenatal visit.

‡Antepartum hemorrhage was defined as bleeding at more than 20 weeks' gestation.

§Active labor was defined as contractions (at least four in 20 minutes) with dilatation of at least 2 cm and 80 percent effacement, in nulliparous women, or dilatation of at least 3 cm, in parous women.

TABLE 3. TREATMENT AND TIMING OF DELIVERY IN THE PHENOBARBITAL AND PLACEBO GROUPS.

VARIABLE	PHENOBARBITAL	PLACEBO	P VALUE
	GROUP (N=309)	GROUP (N=301)	
	no. of women (%)		
Treatment			
Infusion			
Complete	289 (94)	281 (93)	1.00
Incomplete	1 (<1)	5 (2)	0.12
None	19 (6)	15 (5)	0.60
Maintenance dose (≥1)	101 (33)	98 (33)	0.97
Additional bolus infusion on readmission	5 (2)	10 (3)	0.20
Delivery			
Within 24 hr after randomization	194 (63)	191 (63)	0.86
Within 24 hr after infusion	179 (58)	182 (60)	0.52
Within 24 hr after infusion or last maintenance dose	247 (80)	235 (78)	0.33

mode of delivery — vaginal or cesarean, with or without labor — were similar in the two groups.

Pregnancy continued beyond 33 weeks' gestation in 41 women (7 percent): 16 (5 percent) in the phenobarbital group and 25 (8 percent) in the placebo group. A total of 668 infants were delivered to the 610 women: 344 infants in the phenobarbital group and 324 in the placebo group. A total of 664 infants were born alive: 341 in the phenobarbital group and 323 in the placebo group; 322 (94 percent) of the infants in the phenobarbital group and 296 (91 percent) of those in the placebo group had a gestational age of less than 34 weeks.

Administration of the Study Drug

Thirty-four women (19 in the phenobarbital group and 15 in the placebo group) delivered before treatment was initiated (Table 3). The median time from randomization to initiation of treatment was 45 minutes in both groups. The mean duration of the infusion was 28 minutes in the phenobarbital group and 27 minutes in the placebo group. The median time from randomization to delivery was 14 hours in the phenobarbital group (range, 0.3 to 1580) and 12 hours in the placebo group (range, 0.3 to 2238). The median time from the last dose of the study medication to delivery was 10 hours in the phenobarbital group (range, 0.4 to 1383) and 8 hours in the placebo group (range, 0.1 to 1715).

Level of Sedation and Adverse Events

Among the 290 women who received phenobarbital, 31 (11 percent) were alert, 102 (35 percent) were moderately sedated, 67 (23 percent) were very sedated, and 84 (29 percent) fell asleep after administration of the study drug; among the 286 women who received placebo, 162 (57 percent) were alert, 85 (30 percent) were moderately sedated, 13 (5 percent) were very sedated, and 22 (8 percent) fell asleep. Three women in the phenobarbital group had respiratory distress not requiring assisted ventilation. In the placebo group, one woman had sepsis, one had respiratory distress, one had uterine hemorrhage, and one had cardiopulmonary collapse. None of these events were considered to be related to the study drug. There were no adverse events involving the infants. Serum phenobarbital concentrations in 81 mother-infant pairs ranged from 7 to 11 µg per milliliter in the phenobarbital group and were less than 1 µg per milliliter in the placebo group.

Characteristics of the Infants

The clinical characteristics of all the infants and of those born before 34 weeks' gestation are shown in Table 4. The characteristics of the infants in the two groups were similar except for sex and the Apgar score at one minute. Similarly, when each pregnancy was evaluated as a single event, there were no signif-

icant differences between the two groups except for sex and the Apgar score at one minute.

Among the infants delivered before 34 weeks' gestation, the phenobarbital and placebo groups were similar with respect to the frequency of respiratory failure (defined as the need for ventilatory support), acidosis (arterial-blood pH, <7.25), hypertension (mean arterial pressure, >65 mm Hg), and hypotension (mean arterial pressure, <20 mm Hg) during the first postnatal week. Similar numbers of infants in the two groups received drugs that might have influenced the incidence of intracranial hemorrhage (phenobarbital, sodium bicarbonate, indomethacin, or sedatives such as morphine, chloral hydrate, fentanyl, and pancuronium bromide). Thirty percent of the infants in the phenobarbital group and 33 percent of those in the placebo group received indomethacin. The frequencies of complications such as patent ductus arteriosus, pneumothorax, and pneumomediastinum were similar in the phenobarbital and placebo groups.

Primary Outcomes

The incidence of intracranial hemorrhage or death within 72 hours after birth was similar in the phenobarbital group (24 percent) and the placebo

group (23 percent) (Table 5). The estimated relative risk of hemorrhage or early death in the phenobarbital group was 1.1 (95 percent confidence interval, 0.8 to 1.4). Among the 590 infants born before 34 weeks' gestation in whom ultrasonographic studies were performed, 70 of 311 (23 percent) in the phenobarbital group and 64 of 279 (23 percent) in the placebo group had intracranial hemorrhages (relative risk, 1.0; 95 percent confidence interval, 0.8 to 1.4). There was no difference in the severity of intracranial hemorrhage between the two groups. The incidence of intracranial hemorrhage or early death was also similar in the two groups when each pregnancy was evaluated as a single event.

Periventricular leukomalacia was detected in 12 infants (4 percent) in the phenobarbital group and 9 infants (3 percent) in the placebo group. Post-hemorrhagic ventriculomegaly was diagnosed in 14 infants in the phenobarbital group and 10 infants in the placebo group. One infant in each group required permanent ventricular drainage with a ventriculoperitoneal shunt.

Assessments at 18 to 22 Months

Of the 578 infants who were born before 34 weeks' gestation and survived until discharge from

TABLE 4. CHARACTERISTICS OF THE INFANTS BORN TO THE WOMEN IN THE PHENOBARBITAL AND PLACEBO GROUPS.*

CHARACTERISTIC	ALL INFANTS			INFANTS BORN BEFORE 34 WEEKS' GESTATION		
	PHENOBARBITAL GROUP (N = 344)	PLACEBO GROUP (N = 324)	P VALUE	PHENOBARBITAL GROUP (N = 325)	PLACEBO GROUP (N = 297)	P VALUE
Live birth — no. (%)	341 (99)	323 (100)	0.63	322 (99)	296 (100)	0.63
Birth weight — g	1402 ± 521	1452 ± 582	0.25	1335 ± 444	1351 ± 480	0.67
Gestational age — wk	31 ± 3	31 ± 3	0.32	30 ± 3	30 ± 3	0.69
Female sex — no. (%)	181 (53)	144 (44)	0.03	168 (52)	129 (43)	0.04
Apgar score ≤ 3 — no. (%)						
At 1 min	79 (23)	50 (15)	0.01	78 (24)	48 (16)	0.02
At 5 min	22 (6)	14 (4)	0.30	22 (7)	14 (5)	0.31
Intubation in delivery room — no. (%)	171 (50)	145 (45)	0.20	170 (52)	144 (48)	0.36
Administration of drugs in delivery room — no. (%)	34 (10)	20 (6)	0.09	34 (10)	20 (7)	0.12
Treatment with surfactant in first 24 hr — no. (%)	119 (35)	102 (31)	0.39	117 (36)	102 (34)	0.67
Mechanical ventilation in first 24 hr — no. (%)				197 (61)	169 (57)	0.38
Days on ventilator						0.72
Median				2	2	
Range				0–173	0–220	
Pneumothorax — no. (%)				13 (4)	9 (3)	0.52
Survival to discharge — no. (%)	316 (92)	307 (95)	0.18	298 (92)	280 (94)	0.21
Days in hospital			0.96			0.48
Median	38	39		39	42	
Range	1–244	1–385		1–244	1–385	

*Plus-minus values are means ±SD.

TABLE 5. EFFECT OF ANTENATAL ADMINISTRATION OF PHENOBARBITAL ON NEONATAL OUTCOME.

OUTCOME	PHENOBARBITAL GROUP (N=344)	PLACEBO GROUP (N=324)	P VALUE
	no. of infants (%)		
All infants			
Live birth	341 (99)	323 (100)	0.63
Death in first 72 hr, including stillbirth	14 (4)	10 (3)	0.54
Intracranial hemorrhage or death in first 72 hr	83 (24)	74 (23)	0.69
Infants born before 34 weeks' gestation			
Intracranial hemorrhage*	70 (23)	64 (23)	0.90
Grade I	45 (14)	42 (15)	
Grade II	13 (4)	15 (5)	
Grade III	4 (1)	3 (1)	
Grade IV	8 (3)	4 (1)	
Periventricular leukomalacia*	12 (4)	9 (3)	0.83

*Data are based on ultrasonographic studies, which were performed in 311 of the infants in the phenobarbital group and 279 of those in the placebo group.

the neonatal intensive care unit, 422 (73 percent) were assessed at 18 to 22 months; 7 infants died after discharge from the neonatal intensive care unit, 125 were lost to follow-up, and 24 had not yet been evaluated at this writing. The mean (\pm SD) score on the Bayley II Mental Developmental Index was 84 ± 17 in the 218 infants in the phenobarbital group and 85 ± 16 in the 204 infants in the placebo group. The mean score on the Bayley II Psychomotor Developmental Index was 88 ± 17 in the phenobarbital group and 89 ± 17 in the placebo group. The incidence of cerebral palsy was 9 percent in the phenobarbital group and 8 percent in the placebo group.

DISCUSSION

In premature infants born before 34 weeks' gestation, fluctuations in blood flow, particularly within the vascular network of the periventricular germinal matrix, increase the risk of intracranial hemorrhage. Phenobarbital abolishes the hypertensive peaks that occur during spontaneous activity and clinical procedures in premature neonates.¹⁵ In newborn animals with induced hypertension, pretreatment with phenobarbital reduces the frequency of neonatal intracranial hemorrhage.¹⁶

The first studies of antenatal phenobarbital therapy showed that it was effective in decreasing the frequency of neonatal intracranial hemorrhage and death.⁵⁻⁹ In contrast, we found that antenatal administration of phenobarbital did not reduce the incidence of intracranial hemorrhage or early death in infants with a gestational age of less than 34 weeks. Our randomized, placebo-controlled study involved

a larger group of infants than those in previous studies (668 vs. 38 to 150).

An additional strength of our trial was the selection of participants; fewer women delivered after 34 weeks' gestation (when the risk of intracranial hemorrhage decreases) than in previous studies.^{5,8,9} Moreover, in our study the demographic and perinatal characteristics of the women in the phenobarbital and placebo groups were similar, whereas in previous studies, the mode of delivery and the frequency of antenatal corticosteroid therapy differed between the groups.^{5,6} In our study, 59 percent of the women in the phenobarbital group and 58 percent of those in the placebo group received antenatal corticosteroid therapy, which provides protection against neonatal intracranial hemorrhage.¹⁷ The characteristics of the infants in the two groups were similar, except that there were more female infants in the phenobarbital group; female sex has been shown to be associated with a lower risk of neonatal intracranial hemorrhage than male sex.¹⁸ In previous studies, there were differences in sex and other characteristics that affect the risk of intracranial hemorrhage, such as the presence or absence of the respiratory distress syndrome and the volume of fluids administered.^{5,7,8}

The results of two somewhat similar trials of the effect of antenatal phenobarbital therapy on neonatal intracranial hemorrhage have been published since the completion of our trial. In one trial, antenatal administration of phenobarbital combined with vitamin K did not reduce the frequency or severity of intracranial hemorrhage in preterm infants.¹⁹ In the other trial, the rate of intracranial hemorrhage was reduced among infants born to women with multiple gestations who had received phenobarbital before delivery.⁹ Women with more than two fetuses were excluded from the current trial, and each pregnancy was evaluated as a single event.

The phenobarbital dosage used in this trial was based on the drug's transplacental kinetics.¹¹ Sedation was the only side effect in the women. The Apgar scores at one minute were lower in the infants exposed to phenobarbital than in the infants exposed to placebo, but the Apgar scores at five minutes were similar in the two groups.

We found that antenatal administration of phenobarbital was not effective in preventing neonatal intracranial hemorrhage, although a meta-analysis of previous studies suggested a benefit.¹ We speculate that overall improvements in care in the perinatal and early neonatal period, including antenatal antibiotic therapy²⁰ and corticosteroid therapy, contributed to the low incidence of all grades of neonatal intracranial hemorrhage. The results of our trial do not support the use of antenatal treatment with phenobarbital as prophylaxis against neonatal intracranial hemorrhage.

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