

PHENOBARBITAL COMPARED WITH PHENYTOIN FOR THE TREATMENT OF NEONATAL SEIZURES

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ABSTRACT

Background Seizures occur in 1 to 2 percent of neonates admitted to an intensive care unit. The treatment is usually with either phenobarbital or phenytoin, but the efficacy of the two drugs has not been compared directly.

Methods From 1990 to 1995, we studied 59 neonates with seizures that were confirmed by electroencephalography. The neonates were randomly assigned to receive either phenobarbital or phenytoin intravenously, at doses sufficient to achieve free plasma concentrations of 25 μg per milliliter for phenobarbital and 3 μg per milliliter for phenytoin. Neonates whose seizures were not controlled by the assigned drug were then treated with both drugs. Seizure control was assessed by electroencephalographic criteria.

Results Seizures were controlled in 13 of the 30 neonates assigned to receive phenobarbital (43 percent) and 13 of the 29 neonates assigned to receive phenytoin (45 percent; $P=1.00$). When combined treatment is considered, seizure control was achieved in 17 (57 percent) of the neonates assigned to receive phenobarbital first and 18 (62 percent) of those assigned to receive phenytoin first ($P=0.67$). The severity of the seizures was a stronger predictor of the success of treatment than was the assigned agent. Neonates with mild seizures or with seizures that were decreasing in severity before treatment were more likely to have their seizures end, regardless of the treatment assignment.

Conclusions Phenobarbital and phenytoin are equally but incompletely effective as anticonvulsants in neonates. With either drug given alone, the seizures were controlled in fewer than half of the neonates. (N Engl J Med 1999;341:485-9.)

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IN neonatal intensive care units seizures occur in 1 to 2 percent of neonates, but there is no agreement concerning either the most appropriate diagnostic tests or the most appropriate treatment for such infants.¹⁻⁵ Most seizures are due to hypoxic ischemic encephalopathy, hemorrhage, or cerebral infarction. The natural history of neonatal seizures is unknown, but observations suggest that the seizures may be most severe in the first week of life and subsequently abate regardless of intervention. The effects of neonatal seizures on brain development are difficult to differentiate from those of the brain lesions causing them, but recent data from studies in animals suggest that seizures themselves are deleterious to the development of the immature brain.^{6,7}

Seizures have often been diagnosed on the basis of clinical findings, but the diagnosis may be inaccurate without electroencephalographic confirmation.^{8,9} Nevertheless, despite concern about diagnosis, most physicians choose to treat neonates who have seizures, most commonly with either phenobarbital or phenytoin,¹⁰ primarily because of the experience with these drugs in older children and adults. Both drugs are thought to be effective in neonates, but there are no data about their efficacy in relation to the clinical and physiologic characteristics of the seizures, and the two drugs have not been compared directly. We therefore conducted a randomized trial to assess the relative efficacy of phenobarbital and phenytoin in the treatment of seizures in neonates, using electroencephalographic criteria for diagnosis and to determine efficacy.

METHODS**Study Subjects**

The study was conducted at the Magee Women's Hospital in Pittsburgh between 1990 and 1995. The protocol was approved by the hospital's institutional review board. We identified neonates in the neonatal intensive care unit who were at risk for seizures because of reported abnormal movements; an Apgar score of less than 5 at five minutes with a base deficit of more than 10 mmol per liter; traumatic delivery; maternal exposure to nonprescription narcotic drugs, amphetamines, or barbiturates; or central nervous system infection or malformation. When a neonate was identified as meeting one or more of these criteria, written informed consent was obtained from a parent and the infant was enrolled in the study. Neonates with associated pulmonary, hepatic, renal, or cardiac dysfunction were not excluded, and most babies received antibiotics, diuretics, hyperalimentation, albumin, or a combination of these therapies.

Electroencephalographic Monitoring

At the time of enrollment, a standard 21-channel electroencephalogram was obtained. A seizure was defined as an episode lasting at least 10 seconds and consisting of a succession of abnormal repetitive electrical discharges with demonstrable onset, wave-form morphology, and amplitude. If no electrical seizures were detected at the time of enrollment, one-hour electroencephalograms were obtained on each of the next two days. If electrical seizures were detected on any electroencephalogram, the neonate was randomly assigned to receive one of the two anticonvulsant drugs. All of the neonates had continuous electroencephalographic recordings for 24 hours, starting from the time of the electroen-

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cephalogram that determined their eligibility for the trial, or until both drugs had proved to be ineffective. Electroencephalographic technicians were present throughout the entire recording period to monitor the technical adequacy of the tracings.¹¹

Treatment Protocol

The infants were randomly assigned to treatment with phenobarbital or phenytoin according to a block design to ensure balanced treatment assignment over time with respect to race and gestational age. The study was single-blinded, in that the physicians, hospital staff, and electroencephalographic technicians were aware of the treatment assignments.

Phenobarbital and phenytoin were administered intravenously over a 5-to-15-minute period once daily. The doses of phenobarbital and phenytoin needed to achieve plasma concentrations of free drug of 25 and 3 μg per milliliter, respectively, were calculated by a formula that accounts for the volume of distribution and protein binding of drugs.¹² Plasma free drug concentrations were measured 30 minutes after the first dose. If the target concentrations had not been achieved, an additional dose was administered, and the assessment process was repeated. The peak plasma concentrations of free phenobarbital and phenytoin were measured for the first 24 hours after administration by high-performance liquid chromatography after ultracentrifugation.¹²

Subsequently, trough plasma concentrations of free drug were measured twice daily, and drug doses were adjusted so that the plasma concentrations of free phenobarbital and phenytoin were at least 22.5 and 2.5 μg per milliliter, respectively. Treatment was considered to have failed if the neonate had an episode of electrical seizures lasting longer than 2.5 minutes or a total of 2.5 minutes of seizure activity during any 5-minute period. When treated with one drug failed, the second drug was added. Therapy was discontinued after seven days if the neonate did not have abnormal movements suggesting seizure. If clinical seizures persisted beyond seven days or resumed after therapy had been discontinued, the attending physician decided whether to use another anticonvulsant.

The heart rate and rhythm, mean arterial pressure, and respiratory status were monitored continuously during treatment. In neonates who did not have arterial lines placed, blood pressure was measured by Doppler ultrasonography every 15 minutes for the first hour and hourly thereafter during treatment. Arrhythmia was defined as a clinically important alteration in rhythm, as judged by the attending neonatologist. Bradycardia was defined as a heart rate of less than 80 beats per minute. Hypotension was defined as a mean arterial pressure of less than 25 mm Hg in neonates weighing less than 500 g, less than 30 mm Hg in neonates weighing 501 to 1500 g, less than 35 mm Hg in neonates weighing 1501 to 2000 g, less than 40 mm Hg in neonates weighing 2001 to 3000 g, and less than 45 mm Hg in neonates weighing more than 3000 g. Apnea was defined as an interval of more than 20 seconds between breaths. Infants who had arrhythmia, bradycardia, hypotension, or apnea were withdrawn from the study.

Characterization of Seizures and Study Periods

Seizures during treatment were characterized with respect to duration and severity, as determined by electroencephalography. The duration was calculated as the elapsed time from the detection of epileptiform activity in one or more electroencephalographic channels to complete cessation of epileptiform activity. The severity of individual seizures was calculated as the duration of epileptiform activity in each channel, summed across all channels that were active during that seizure and expressed as channel-seconds (one channel-second equals one second of activity in a single channel).

Five study periods were defined: from the initiation of the electroencephalographic monitoring that established eligibility to administration of the study drug (period 1); from the end of period 1 to the time at which the predetermined plasma concentrations of free drug were first achieved (period 2); from the end of period

2 to the time at which the second drug was added or, if no further seizures occurred, to the end of the study period (period 3); from the end of period 3 to the time at which the target plasma free concentration of the second drug, if added, was achieved (period 4); and from the end of period 4 to 24 hours after the initiation of electroencephalographic monitoring if no seizures occurred, or to the time at which failure of therapy was determined (period 5). Neonates in whom treatment was considered successful with one drug had three study periods, whereas those who received two drugs had five study periods. The severity of seizures during each period was calculated by summing the severity scores for all seizures occurring within that period; severity per hour (expressed as channel-seconds per hour) was calculated by dividing the severity score by the duration of the period.

End Points

The primary end point was the complete control of seizures, as determined by electroencephalographic recording, during treatment with one drug or after the addition of the second drug. The occurrence of any electrical seizure after target plasma concentrations of free drug had been achieved was considered to indicate treatment failure for that drug. If, after target plasma concentrations of the first drug had been achieved, a neonate had continuous electrical seizure activity for 2.5 minutes or had 2.5 minutes of seizure activity in any 5-minute period, the attending neurologist was called and the electrical seizure was confirmed. Treatment with the other drug was then initiated. Thus, if a neonate had a short seizure (less than 2.5 minutes) while being treated with one drug, the treatment could be classified as a failure, even though the second drug was not added.

We also arbitrarily defined success as an 80 percent reduction in the severity of seizures (calculated as the mean severity per hour) in period 3, or period 5 for neonates receiving both drugs, as compared with the severity in period 1.

Statistical Analysis

We conducted two intention-to-treat analyses. First, we tested whether the two drugs differed in their ability to control seizures when administered as single therapy, and second, we tested whether the ability of two drugs to control seizures was dependent on the sequence of administration. Because seizures resolve spontaneously in some neonates, we derived a measure of self-resolution by computing the slope of the plot of seizure severity against time in period 1, as defined above, by dividing the period into 10 equal intervals and calculating the total severity of seizures during each interval. We then determined the severity of seizures as a function of time for each neonate, generating a trend, expressed as channel-seconds per hour per period. The study population was divided into approximately equal groups according to slopes of +600 and -600 channel-seconds per hour per period. Trends in the severity of seizures were classified as increasing (greater than +600), indeterminate (-600 to +600), or decreasing (less than -600) on the basis of the direction and strength of the slope. We tested whether either drug was effective against seizures of decreasing, indeterminate, or increasing severity. We used Fisher's exact test and the chi-square test to compare categorical variables. All data analyses were performed with SPSS software (SPSS, Chicago), and all statistical tests were two-tailed.

RESULTS

Of 157 neonates screened for enrollment, 59 had epileptiform activity on electroencephalograms and were enrolled in the study. Thirty were assigned to receive phenobarbital and 29 to receive phenytoin. The treatment groups were similar with respect to gestational age, race, and cause of seizures, but there were significantly more girls in the phenobarbital group (Table 1).

TABLE 1. CHARACTERISTICS OF NEONATES IN A RANDOMIZED TRIAL OF PHENOBARBITAL AND PHENYTOIN FOR THE TREATMENT OF SEIZURES.

CHARACTERISTIC	PHENOBARBITAL (N=30)	PHENYTOIN (N=29)	P VALUE
	no. (%)		
Gestational age (wk)			0.47*
≤28	4 (13)	1 (3)	
29–32	2 (7)	3 (10)	
33–37	5 (17)	6 (21)	
>37	19 (63)	19 (66)	
Sex			0.02†
Male	14 (47)	22 (76)	
Female	16 (53)	7 (24)	
Race			0.92‡
White	19 (63)	18 (62)	
Black	10 (33)	10 (34)	
Asian	1 (3)	1 (3)	
Primary cause of seizure			0.08§
Asphyxia, hemorrhage, or infarction	22 (73)	27 (93)	
Central nervous system malformations	4 (13)	0 (0)	
Central nervous system infection	2 (7)	1 (3)	
Undetermined	2 (7)	1 (3)	

*The chi-square test was used to compare the distribution of gestational ages of less than 33 weeks, 33 to 37 weeks, and more than 37 weeks between the treatment groups.

†The chi-square test was used to compare the distribution of boys and girls between the treatment groups.

‡The chi-square test was used to compare the distribution of white and nonwhite neonates between the treatment groups.

§Fisher's exact test was used to compare the distribution of asphyxia, hemorrhage, or infarction and all other causes between the treatment groups.

Electrical Seizure Activity

The control of electrical seizures was similar in the two groups (Fig. 1). Among the 30 neonates assigned to receive phenobarbital, the seizures were completely controlled in 13 (43 percent), as compared with 13 of the 29 neonates in the phenytoin group (45 percent, P=1.00 by Fisher's exact test).

Among the 17 neonates in the phenobarbital group in whom the seizures were not completely controlled, 15 were given phenytoin, with complete control of seizures in 4. Thus, in 17 of the 30 neonates in the original phenobarbital group (57 percent), the seizures were completely controlled by one or both drugs. Among the 16 neonates in the phenytoin group in whom the seizures were not completely controlled, 13 were given phenobarbital, with complete control of seizures in 5. The overall success rate in the phenytoin group was 62 percent (18 of 29 neonates). The difference of 5 percentage points (95 percent confidence interval, -20 to 30) was not significant (P=0.67).

Seven additional neonates in the phenobarbital group had an 80 percent reduction in seizures, so that, overall, 24 of the 30 neonates in this group (80 percent) had substantial improvement. In the phenytoin group, 3 neonates had an 80 percent reduction, giving an overall rate of improvement of 72 percent (21 of 29 neonates, P=0.30 by Fisher's exact test).

The severity of seizure activity during period 1 was strongly inversely related to the successful control of seizures (Table 2). Among the 10 neonates who had seizures averaging 20,000 or more chan-

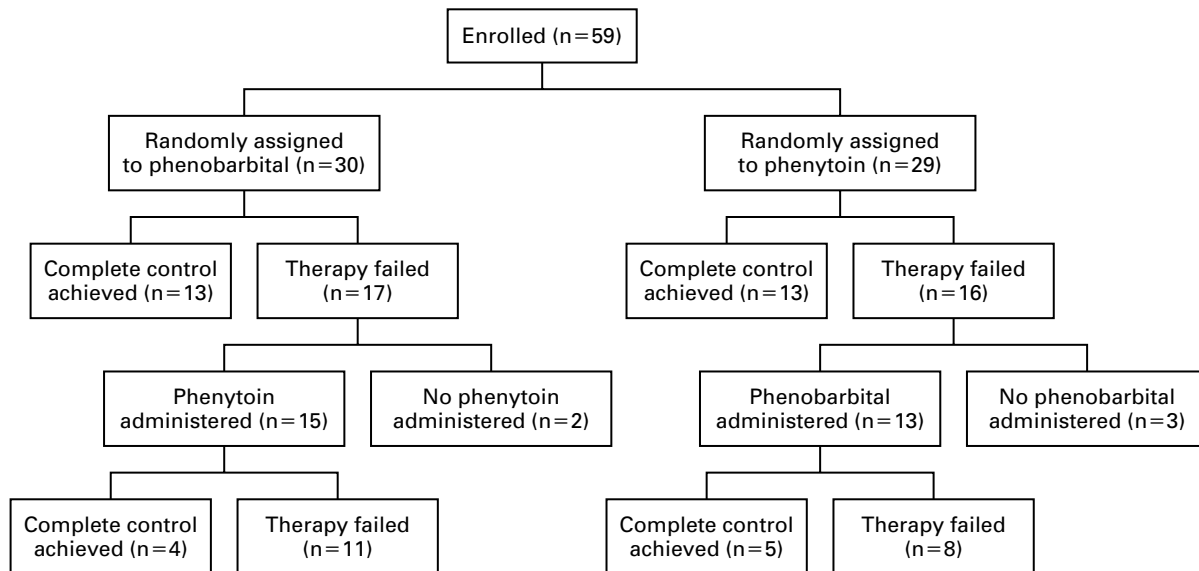


Figure 1. Treatment Assignment and Outcomes of 59 Neonates with Seizures Treated with Phenobarbital or Phenytoin.

TABLE 2. OUTCOME OF TREATMENT OF SEIZURES IN NEONATES ACCORDING TO THE SEVERITY OF SEIZURES BEFORE TREATMENT.*

VARIABLE	GROUP SIZE	COMPLETE SEIZURE CONTROL	P VALUE FOR TREND	≥80% SEIZURE CONTROL	P VALUE FOR TREND
		no. (%)		no. (%)	
Severity of index seizure			<0.001		0.002
Mild (≤3000 channel-seconds)	17	15 (88)		16 (94)	
Moderate (3001–19,999 channel-seconds)	32	19 (59)		25 (78)	
Severe (≥20,000 channel-seconds)	10	1 (10)		4 (40)	
Trend in severity of seizures			0.001		<0.001
Decreasing	21	17 (81)		20 (95)	
Indeterminate	18	12 (67)		15 (83)	
Increasing	20	6 (30)		10 (50)	

*The chi-square test for trend was used to determine the P values.

nel-seconds per hour during period 1, the seizures were successfully controlled in 1 (10 percent), as compared with 15 of the 17 neonates (88 percent) who had the least severe seizures during period 1 (P for linear trend <0.001). The initial drug treatment did not affect this association (data not shown).

The trend in the severity of seizures was also a determinant of treatment success. Among 20 neonates with an increasing slope, the seizures were controlled in 6 (30 percent), as compared with 12 of 18 with an indeterminate slope (67 percent) and 17 of 21 with a decreasing slope (81 percent) (P for linear trend=0.001). Again, the initial drug treatment did not affect this association (data not shown).

Clinical Seizure Activity

Eight neonates could not be assessed clinically because they were given neuromuscular blocking drugs after enrollment. Of the remaining 51 neonates, 3 (6 percent) had electrical seizures but no clinical seizures during the study, and 48 had clinical as well as electrical seizures. Among these 48 neonates, treatment with one or both drugs failed in 20, among whom 5 had only electrical seizures and 15 had both electrical and clinical seizures.

Adverse Effects

There were no changes in heart rate, heart rhythm, mean arterial pressure, or respiratory status that could be related to the plasma concentrations of free phenobarbital or phenytoin.

DISCUSSION

Using electroencephalographic criteria both for diagnosis and to determine the response to treatment, we found that phenobarbital and phenytoin were equally but incompletely effective for the treatment of seizures in neonates. Complete control of seizures was achieved in only 59 percent of the ne-

onates, and the probability of success increased with decreasing severity of the seizure. It is possible that seizures would have been controlled in more infants had higher doses been given.

The choice of the target plasma concentrations of free drug was based on knowledge that the active component is the unbound fraction of each drug. In a previous study,¹³ a heart rate of less than 100 beats per minute was predictably obtained when plasma total phenobarbital concentrations were more than 50 μg per milliliter. On the assumption that 50 percent of phenobarbital is bound to protein in plasma, the free phenobarbital concentration would be 25 μg per milliliter. However, the plasma of neonates binds less phenobarbital than that of older children and adults, so the mean total plasma phenobarbital concentrations in this study approached 40 μg per milliliter.¹² We therefore cannot conclude that higher phenobarbital doses would not be effective. We noted no adverse effects of phenobarbital, and higher plasma concentrations of free phenobarbital might be attained with added efficacy and no toxicity. In giving higher doses of phenobarbital, however, one must consider the evidence from studies in both animals and humans that it may have deleterious effects on the developing brain.^{14,15} We also noted no adverse effects of phenytoin, but we would be reluctant to give higher doses in view of the variability of plasma drug binding and the cardiac toxicity of this drug in neonates.

There is controversy about whether seizures themselves damage the developing brain.⁷ If treatment is indicated, our study shows that phenobarbital and phenytoin at free plasma concentrations of 25 and 3 μg per milliliter, respectively, are equally but poorly effective. Neonates with seizures have also been treated with benzodiazepines, but in most studies, these drugs have been given as adjunctive therapy, and efficacy has not been assessed in controlled studies us-

ing electroencephalographic diagnosis.¹⁶⁻¹⁹ The effectiveness of phenobarbital and phenytoin in treating neonatal seizures is disappointing, but we cannot conclude on the basis of this study that these drugs are entirely ineffective. Development of a safe and effective treatment strategy for neonates with seizures is an important priority for future research.

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