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Single Enteral Loading Dose of Phenobarbital for Achieving Its Therapeutic Serum Levels in Neonates

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Aim To investigate whether therapeutic serum drug levels may be achieved with a single enteral loading dose of phenobarbital.

Methods The study was performed at the Mersin University Hospital in Turkey between April 2004 and August 2006, and included 29 newborn babies with seizure. After the acute treatment of the seizure with midazolam at a dose of 0.1 mg/kg, phenobarbital was administered by orogastric route at a loading dose of 20 mg/kg. Serum phenobarbital concentrations were measured at 0.5, 3, 6, and 12 hours after the loading. Serum phenobarbital levels between 10-30 μg/mL were considered as the therapeutic range.

Results The serum phenobarbital levels reached therapeutic values in 9 (31%), 19 (66%), 21 (72%), and 23 (79%) patients at 0.5, 3, 6, and 12 hours after loading, respectively, while they did not reach therapeutic values in 6 patients (21%) after 12 hours. Four of the patients in whom there was no increase in serum phenobarbital levels had hypoxic-ischemic encephalopathy.

Conclusion Enteral loading of phenobarbital can achieve therapeutic serum levels in the large majority of newborn babies with seizure and may be safely used in babies with the intact gastrointestinal tract.

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Seizures are the most common neurological emergency in newborn babies, in whom they occur more frequently than in adolescents or adults. The incidence of neonatal seizures varies between 0.1% and 8.6% (1-5) and depends in part on the gestational age and the nature of the studied population. The long-term outcome of infants with seizures has been associated primarily with the cause of seizures, but reports on both laboratory animals and newborn infants suggest that seizures themselves may have a deleterious effect (6-10). Although phenobarbital is commonly accepted as the first-choice treatment for seizures in newborns, there is no consensus regarding the most appropriate treatment (11-13). There is considerable evidence that phenobarbital achieves clinical and electrographic control in one third to one half of babies within a few hours, and most physicians choose it to treat neonates with seizures (11-15).

Studies evaluating the efficacy of phenobarbital have been done using the intravenous form of the drug and all therapeutic recommendations have been based on the data obtained from these studies. Seizure is usually treated with a single intravenous dose of midazolam in the acute period, followed by intravenous administration of phenobarbital, and the treatment is continued with intravenous phenytoin. Unfortunately, intravenous formulations of phenobarbital are not available in some countries, and intravenous phenytoin loading or midazolam infusion is usually the first choice of second line antiepileptic drugs. In some of these countries, phenobarbital is typically administered by enteral loading, but as far we know, no study has been published evaluating the efficacy of this method. The aim of this study was to investigate whether enterally loaded phenobarbital reaches therapeutic serum levels in newborn babies with seizure.

METHODS

The study was conducted between April 2004 and August 2006 at the Neonatal Intensive Care Unit of Mersin University Hospital in Mersin, Turkey. After informed consent had been obtained from one of the parents, 29 babies with documented clinical or electroencephalographic (EEG) seizures were included. Seizures were treated with midazolam at a dose of 0.1 mg/kg. If the seizure recurred before reaching a therapeutic serum level of phenobarbital, midazolam therapy was repeated. Following the initial midazolam treatment of seizure, phenobarbital was given by orogastric route at a loading dose of 20 mg/kg. Serum phenobarbital concentrations were measured 4 times, at 0.5, 3, 6, and 12 hours after the loading dose. The treatment outcome was defined as achieving the therapeutic serum levels of phenobarbital. It has been suggested that the effective serum concentration range of phenobarbital for neonatal seizures is 10-30 μg/mL (16). Serum phenobarbital levels were measured by the fluorescence polarization method (Cobas Integra 800, Roche Diagnostics, Mannheim, Germany), according to the manufacturer's instructions.

The occurrence of any electrical or clinical seizure at any time after reaching the therapeutic serum level of phenobarbital was considered as treatment failure. In this case, phenytoin was given intravenously at a loading dose of 20 mg/kg as the second anticonvulsant drug.

All of the patients were evaluated for any intracranial pathology by cranial ultrasonography, computerized tomography, or magnetic resonance imaging techniques. Standard electroencephalography was performed on all patients soon after loading phenobarbital and then as needed. Electrical seizure was defined as an episode lasting at least 10 seconds and consisting of a succession of repetitive, abnormal electrical discharges with demonstrable onset, wave-form morphology, and amplitude (14).

Statistical analyses were performed using SPSS for Windows, version 11.0 (SPSS, Inc., Chicago, IL, USA). The baseline characteristics of the study population were described using frequency and descriptive analysis.

RESULTS

A total of 29 patients were enrolled in this study, 18 (62%) of whom were male. Their mean gestational age was 36 ± 3.1 weeks with a mean birth weight of 3033 ± 780 g (Table 1). Their primary diagnoses were hypoxic ischemic encephalopathy (HIE, 41%), malformations of the central nervous system (CNS, 14%), CNS infection (10%), and intracranial hemorrhage (3.4%; Table 1). Abnormal EEG findings were present in 55% of patients.

Serum phenobarbital reached therapeutic serum levels in 9 (31%), 19 (66%), 21 (72%), and 23 (79%) of 29 patients at 0.5, 3, 6 and 12 hours after the loading dose, respectively (Table 2), while they did not reach therapeutic levels in only 6 patients (21%) at the end of 12 hours, 4 of whom had HIE. Serum phenobarbital levels were found to be close to the lower limit of the therapeutic range in 2 patients (9.6 and 9.1 μg/mL).

TABLE 1. Baseline patients' characteristics*

Characteristic	
Gestational age (weeks), mean ± SD (min-max)	36.1 ± 3.0 (29-40)
Birth weight (grams), mean ± SD (min-max)	3033 ± 780 (1220-4250)
Postnatal age (days), median (25%-75%)	3 (2-10)
Male, % (n)	62 (18)
Primary cause of seizure, % (n):	
HIE	41 (12)
CNS malformations	14 (4)
CNS infection	10 (3)
ICH	3.4 (1)
Other	10 (3)
Undetermined	21 (6)

*Abbreviations: CNS – central nervous system; HIE – hypoxic ischemic encephalopathy; ICH – intracranial hemorrhage; SD – standard deviation.

TABLE 2. Patients achieving therapeutic serum levels of phenobarbital as a function of time after loading dose

Time after oading dose (h)	Patients achieving therapeutic phenobarbital levels (%, n)*	95% confidence interval
0.5	31 (9)	14.19-47.87
3	66 (19)	47.64-82.36
6	72 (21)	55.66-88.34
12	79 (23)	64.18-93.82

*Defined as 10-30 µg/mL (16).

Phenobarbital failed to control seizures in 11 (38%) patients, including the 6 mentioned above who had serum phenobarbital levels below the therapeutic margin. The mean phenobarbital level (±standard deviation) in 11 patients was 14.2 ± 7.4 µg/mL and in 5 patients who had serum phenobarbital levels within the therapeutic range it was 18.5 ± 5.1 µg/mL. Phenytoin was administered to all 11 patients as a second drug.

No acute significant side effects potentially resulting from the antiepileptic drugs (5) were observed, such as hypotension, arrhythmia, and respiratory depression.

DISCUSSION

Our study showed that a single enteral loading dose of 20 mg/kg phenobarbital achieved therapeutic serum levels in the majority of newborn babies with seizure within 12 hours.

Seizures are the most specific symptom of neonatal neurologic insults. In contrast to seizures in an older child, which may be idiopathic or genetic, most neonatal seizures have a specific cause (12). The most frequent causes of neonatal seizures are HIE, intracranial hemorrhage, and infections and abnormalities of the central nervous system (1). HIE was found to be the most common etiologic factor of neonatal seizures in this study. In the majority immature infants, electrical seizures are often not accompanied by clinical seizure activity. Moreover, certain clinical seizures in the newborn consistently fail to appear as EEG seizure activity (1). Such seizures include certain subtle seizures, most generalized tonic seizures, focal and multifocal clonic seizures, and focal and multifocal myoclonic seizures (1). In newborns, seizures may have an epileptic origin, even in the absence of EEG seizure activity (17). In the present study, 55% of clinical seizures in the babies were not consistently accompanied by abnormal EEG. Studies in animals suggest that seizures themselves are deleterious to the development of the immature brain (6-9). Therefore, any suspected clinical seizure activity should be treated, even if the EEG is normal.

Despite the fact that there are very few controlled studies on the medical treatment of neonatal seizures, the usual therapeutic approach involves intravenous administration of benzodiazepine followed by loading and maintenance doses of phenobarbital (3,18). Phenobarbital is still the most commonly preferred first-line drug in the long-term treatment of neonatal seizures (1,11,12,14,15). Since intravenous formulations of phenobarbital are not available in some countries, other intravenous anticonvulsants are usually chosen as the first-line drug.

Phenobarbital is reported to control seizures in almost half of the affected babies (11,17,19). If phenobarbital fails to control the seizure, phenytoin is often recommended as a second-line anticonvulsant drug. Babies with seizure may fail to respond to both antiepileptic drugs. Orman et al (20) has shown that only 33% of neonates responded to the initial phenobarbital loading, with 56% responding to both phenobarbital and phenytoin. In the study by Painter et al (14), complete control of seizures has been achieved in only 59% of the neonates using both phenobarbital and phenytoin. In the present study, phenobarbital failed to control seizures in 38% of the patients. In these cases, phenytoin was used as the second drug.

Phenobarbital is readily and almost completely absorbed after oral administration (21). However, in our study intestines may have been affected by hypoxia and absorption of the drug may have been reduced in babies

with HIE. In such cases, higher or repeated loading doses of phenobarbital may be required to provide therapeutic levels of the drug. Lockman et al (22) has reported that the lowest effective phenobarbital concentration in their study was 16.9 μg/mL. Some authors have observed therapeutic benefits at concentrations up to 40-45 μg/mL (23). Since the mean phenobarbital level in our study was 15 μg/mL, we conclude that higher phenobarbital doses may be more effective.

A potential limitation of our study is the relatively small number of patients treated with phenobarbital. Other limitations of our study are heterogeneity of patient population, the variation in gestational age, and birth weight of patients.

In conclusion, an enteral loading dose of 20 mg/kg phenobarbital achieved therapeutic serum levels in nearly 80% of the newborn babies with clinical or electrical seizure activity within 12 hours. Phenobarbital may safely be given enterally to achieve adequate serum levels in babies without gastrointestinal problems. Higher or repeated loading doses may be required for babies with HIE who may have intestinal absorption problems.

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