Childs Nerv Syst (2013) 29:1353–1357
DOI 10.1007/s00381-013-2094-8

ORIGINAL PAPER

Can we safely administer the recommended dose of phenobarbital in very low birth weight infants?

Osman Oztekin · Salih Kalay · Gonul Tezel · Mustafa Akcakus · Nihal Oygur

Received: 16 January 2013 / Accepted: 22 March 2013 / Published online: 5 April 2013

Abstract
Aim We investigated whether the recommended phenobarbital loading dose of 15–20 mg/kg with maintenance of 3–4 mg/kg/day can safely be administered to very low birth weight preterm newborns with seizures.
Methods Twenty-four convulsive preterms of <1,500 g were enrolled in the study. Phenobarbital was administered intravenously with a loading dose of 15 mg/kg in approximately 10–15 min. After 24 h, the maintenance dose of 3 mg/kg/day was administered as a single injection. Blood samples were obtained 2, 24, 48, 72, and 96 h after the phenobarbital loading dose was administered, immediately before the next phenobarbital dose was injected.
Results None of the cases had plasma phenobarbital concentrations above the therapeutic upper limit of 40 μg/mL on the 2nd hour; one case (4.7 %), on the 24th; 11 cases (45.8 %), on the 48th; 15 cases (62.5 %), on the 72nd; and 17 cases (70.8 %), on the 96th hour. A negative correlation was detected between the serum concentrations of phenobarbital and gestational age on the 72th (p, 0.036; r, −0.608) and 96th hour (p, 0.043; r, −0.769).
Conclusions We suggest that particular attention should be done while administering phenobarbital in preterms, as blood levels of phenobarbital are higher than the reference ranges that those are often reached with the recommended doses in these groups of babies.

Keywords Very low birth weight infant · Seizure · Phenobarbital

O. Oztekin · S. Kalay · G. Tezel · M. Akcakus · N. Oygur (✉)
Department of Pediatrics, Division of Neonatology, Akdeniz University Medical School, 07070, Antalya, Turkey
e-mail: nihaloygur@akdeniz.edu.tr

Introduction

Neonatal seizures are one of the few neonatal neurologic conditions that require immediate medical attention. Phenobarbital and phenytoin remain the most widely used anticonvulsant medications [1, 2]. The half-life of phenobarbital ranges from 45 to 173 h in the neonate; the initial loading dose is recommended as 15–20 mg/kg, with a maintenance dose of 3 to 4 mg/kg per day. This dose is necessary to achieve clearly measurable anticonvulsant effect in the newborn which is consistent with a blood level of approximately 20 μg/mL [3]. Weight or gestational age does not appear to influence the dose–blood level relationship although infants of <30 weeks gestation may require slightly lower doses to achieve the same blood level. Therapeutic levels are usually suggested to range from 15 to 40 μg/mL, although there is no consensus with respect to drug maintenance dosage [4, 5].

Phenobarbital is the most widely used drug to control seizures, and similar loading doses are administered for all gestational ages. However, it is not clear whether the recommended loading dose can safely be administered also to preterms due to gestational age or birth weight. Therefore, the aim of this study was to investigate if it is suitable to administer the same loading dose of phenobarbital in very low birth weight (VLBW) preterm newborns with seizures.

Methods

This study was conducted between January 2010 and March 2011, in the neonatal intensive care unit of Akdeniz University Faculty of Medicine Hospital. Preterm infants with <1,500 g and received phenobarbital for seizure activity were enrolled to the study. Ethical approval was obtained from the institutional review board of the University Hospital of Akdeniz

(Turkey), and written informed consent was obtained from the parents before the study. Neonates, who had additional seizure activity and needed to administer a second dose of phenobarbital or a second drug for the treatment of seizure, were excluded from the study. Patients with alanine aminotransferase (ALT), aspartate aminotransferase (AST), BUN, and creatinine blood levels, exceeding their reference ranges due to gestational age, and albumin level with <2.5 mg/dL or patients receiving drugs that change the serum concentration of phenobarbital were also excluded. Furthermore, small and large for gestational age preterms, patients with pulmonary–cardiac–hepatic and renal congenital anomalies, and whose mothers used antiepileptic drug were excluded from the study.

Amplitude integrated EEG (aEEG) could not be carried out in these infants during acute seizure activity as we do not have aEEG in our NICU; therefore, diagnosis of seizure was determined based on clinical signs of seizures as repetitive buccolingual movements, orbital–ocular movements, unusual bicycling or peddling (subtle seizures), tonic focal or generalized, myoclonic focal or generalized contractions of muscle groups, and flexor/extensor spasms. Patients considered with seizures activity were administered phenobarbital regardless of ventilator support, feeding status, and the treatment of other drugs, except those receiving drugs which change the serum concentration of phenobarbital. Phenobarbital was administered by intravenous (iv) route. Bolus injection of 15 mg/kg sodium phenobarbital was given as a loading dose, over approximately 10–15 min. After 24 h of loading dose, the maintenance dose of 3 mg/kg/day was administered as a single iv injection. All infants received the drug by iv route throughout the study period.

Blood samples were obtained from all infants at 2, 24, 48, 72, and 96 h after the phenobarbital loading dose was administered and immediately before the next phenobarbital dose was injected. The serum concentration of phenobarbital was determined by the kinetic interaction of microparticles in solution known as fluorescence polarization method (Cobas Integra 400 plus, Roche Diagnostic, Mannheim, Germany) according to the manufacturer's instructions. Therapeutic levels of phenobarbital were accepted to range from 15 to 40 μg/mL. Therefore, patients whose blood levels of phenobarbital were of >40 μg/mL were discontinued the treatment.

Patients were followed for the side effects of phenobarbital, including sedation, respiratory depression, hypotension, and bradycardia. Therefore, heart rate and rhythm, mean arterial pressure, and respiratory status were monitored continuously during the treatment period. Bradycardia was defined as a heart rate of less than 100 beats per min. Hypotension was defined as a mean arterial pressure of less than 25 mmHg in neonates weighing <500 g and less than 30 mmHg in neonates weighing between 501 and 1,500 g. Apnea was defined as an interval of more than 20 s between breaths.

Statistical analysis

Patient characteristics were summarized using mean (SD). Changes over time in phenobarbital serum concentrations were analyzed using analysis of variance for repeated measures. The relationship between gestational age, birth weight, and phenobarbital serum concentrations were determined with Pearson correlation coefficients (r). All analyses were done using SPSS for Windows version 18.0 (SPSS, Inc., Chicago, IL, USA). Regression analysis was carried out using the GraphPad Prism 5.0 software. A p value of <0.05 was considered statistically significant.

Results

Thirty-eight preterm infants of <1,500 g with neonatal seizure were admitted to NICU in Akdeniz University Hospital during the study period. Six neonates with associated hepatic–renal dysfunction or an albumin level of <2.5 mg/dL and eight neonates who had additional seizure activity and needed to administer a second dose of phenobarbital or a second drug were excluded from the study. Therefore, 24 preterm infants of <1,500 g were enrolled. Mean gestational age of the patients was 27.17±2.33 weeks with a mean birth weight of 951.29±285.74 g. Serum ALT, AST, BUN, and creatinine levels were 35.58±16.88 IU/L, 36±15.89 IU/L, 24.04±7.11 mg/dL, and 0.74±0.26 mg/dL, respectively.

Out of 24 preterms, 14 had generalized clonic seizure; 1, subtle; 4, generalized tonic; 2, focal clonic; and 3 infants' seizures were unclassified. Perinatal asphyxia in five cases, intraventricular hemorrhage in eight, white matter injury in five, and central nervous system infection in two infants were determined as the primary diagnosis. Etiology could not be found in four of them. Nine infants had more than one etiology, and none had an isolated metabolic disorder as an etiologic factor. The onset time of the treatment was 6.8±5.0 postnatal days (Table 1).

None of the cases had serum phenobarbital concentrations above 40 μg/mL at the 2nd hour; only one case (4.7 %), at the 24th hour; 11 cases (45.8 %), at the 48th; 15 cases (62.5 %), at the 72th; and 17 cases (70.8 %), at the 96th hour. A significant increase was detected for the serum concentrations of phenobarbital, after phenobarbital administration (p, 0.009). A negative correlation was detected between serum concentrations of phenobarbital and the gestational age of infants at the 72th (p, 0.036; r, −0.608) and the 96th hours (p, 0.043; r, −0.769) (Fig. 1a, b). There was no correlation between the serum concentrations of phenobarbital and the birth weight of infants.

During treatment, infusion of vasoactive drug (dopamine 5–10 μg/kg/min) was started in seven preterms for circulatory support or hypotension at the second hour of their postnatal

Table 1 Baseline patients' characteristics

Characteristic	
Gestational age (weeks)[a]	27.17±2.33 (24–32)
Birth weight (grams)[a]	951.29±285.74 (510–1,484)
Male/female	15/9
Onset time of treatment (days)[a]	6.88±5.00 (1–26)
Heart rate/min[a]	124±11.51 (98–156)
Mean arterial pressure (mmHg)[a]	28.95±4.92 (17–38)
Primary cause of seizure, % (*n*)	
Perinatal asphyxia	20.8 (5)
Intraventricular hemorrhage	33.3 (8)
White matter injury	20.8 (5)
Central nervous system infection	8.3 (2)
Undetermined	16.6 (4)

[a] Mean ± SD (min–max)

life. However, their need for inotropic agent was not related with the side effects of phenobarbital. Their seizure activity was detected, while they were administering vasoactive drug, and phenobarbital was given in a few hours after dopamine infusion in all of them. Two preterms had apnea attacks during phenobarbital treatment. However, phenobarbital blood levels were found in normal ranges at the time of apnea attacks in both of them. Two patients died. One of them had a severe intracranial hemorrhage and died on the third day of phenobarbital treatment. In his postmortem evaluation, phenobarbital blood level was 56.3 μg/mL. The other preterm was 24 weeks of gestation and died because of pulmonary hemorrhage. Phenobarbital blood level was 22.6 μg/mL. Additionally, no changes in heart rate, heart rhythm, mean arterial pressure, or in respiratory status were detected in other patients during the study period, which could be related to high plasma concentrations of phenobarbital.

Discussion

During the last 2 or 3 years, some studies have suggested that newer agents, such as levetiracetam and topiramate, seem to be good candidates for the treatment of neonatal seizures. However, data about their efficacy, side effect profiles, and pharmacokinetic properties are limited in newborns [6–10]. Phenobarbital is still the most frequently used anticonvulsant drug for neonatal seizures. In a recent study, phenobarbital was also found as the most widely used first-line medication between 193 participants that responded to the questionnaire, and no differences were apparent for term versus preterm neonates [11]. It is generally recommended to administer that drug with iv routes with a loading dose of 15–20 mg/kg and a maintenance dose of 3 mg/kg/day [3, 4]. Although, it is the first choice of drug for neonatal seizures, there is little information about its doses and safety for preterm newborns. Therefore, we have evaluated whether the recommended phenobarbital loading dose is safe or not for very low birth weight preterm infants with seizures.

In the present study, our results demonstrated that, particularly in preterm infants, it is not suitable to administer the current recommended phenobarbital loading and maintenance doses those for both term and preterm babies. Since, the recommended doses frequently increase to the blood concentrations which are higher than the recommended therapeutic range in preterm infants that may be a leading cause of some adverse affects. Additionally, our results indicated that serum phenobarbital concentrations are rising in course of time after administration. As none of the cases had serum phenobarbital concentrations above 40 μg/mL at the 2nd hour of administration, there was only one case (4.7 %) at the 24th, but this number increased to 11 cases (45.8 %) at the 48th, 15 cases (62.5 %) at the 72th, and 17 cases (70.8 %) at the 96th hour of administration in our study. Therefore, attending physicians in NICU should be aware of that a significant increase with time was detected in serum phenobarbital concentrations after phenobarbital administration, especially in preterm infants.

Moreover, some studies have performed about usage of phenobarbital in preterm infants. Nahat et al. [12] reported that initial maintenance dose during the first month of life was 3.5–4.5 mg/kg/day for preterms with a gestational age of ≤35 weeks and 4–5 mg/kg/day for >35 weeks. Gherpelli et al. [13] conducted a study with a small sample size of 11 preterm (<2,500 g) and 14 term newborns (>2,500 g). They administered iv phenobarbital with a mean of 19.4 mg/kg loading dose, and they have reported that there was no difference in plasma phenobarbital levels between term and preterm newborns. They suggested that a mean loading iv dose of 20 mg/kg was adequate for achievement of therapeutic plasma levels in most infants, in the first 24 h, both in term and preterm infants. In the present study, our study population was smaller than their study population; therefore, we indicated that even the smaller loading dose of phenobarbital enriches to higher blood levels more than therapeutic plasma levels of that drug. We suggest that loading dose of phenobarbital for preterms may be instituted for particularly small preterm infants (<1,500 g).

Protein binding is lower in the newborns (33 %) than that in the older children and adults (41 %); thus, free levels of the drug are relatively higher in the newborn infants that cause decreased binding capacity of that drug [5]. Drug binding in neonates with seizures may change in a sick neonate with organ dysfunction, and toxic side effects may result from elevated free fractions of a drug which adversely affect especially cardiovascular and respiratory functions. To avoid the untoward effects, both total and free antiepileptic

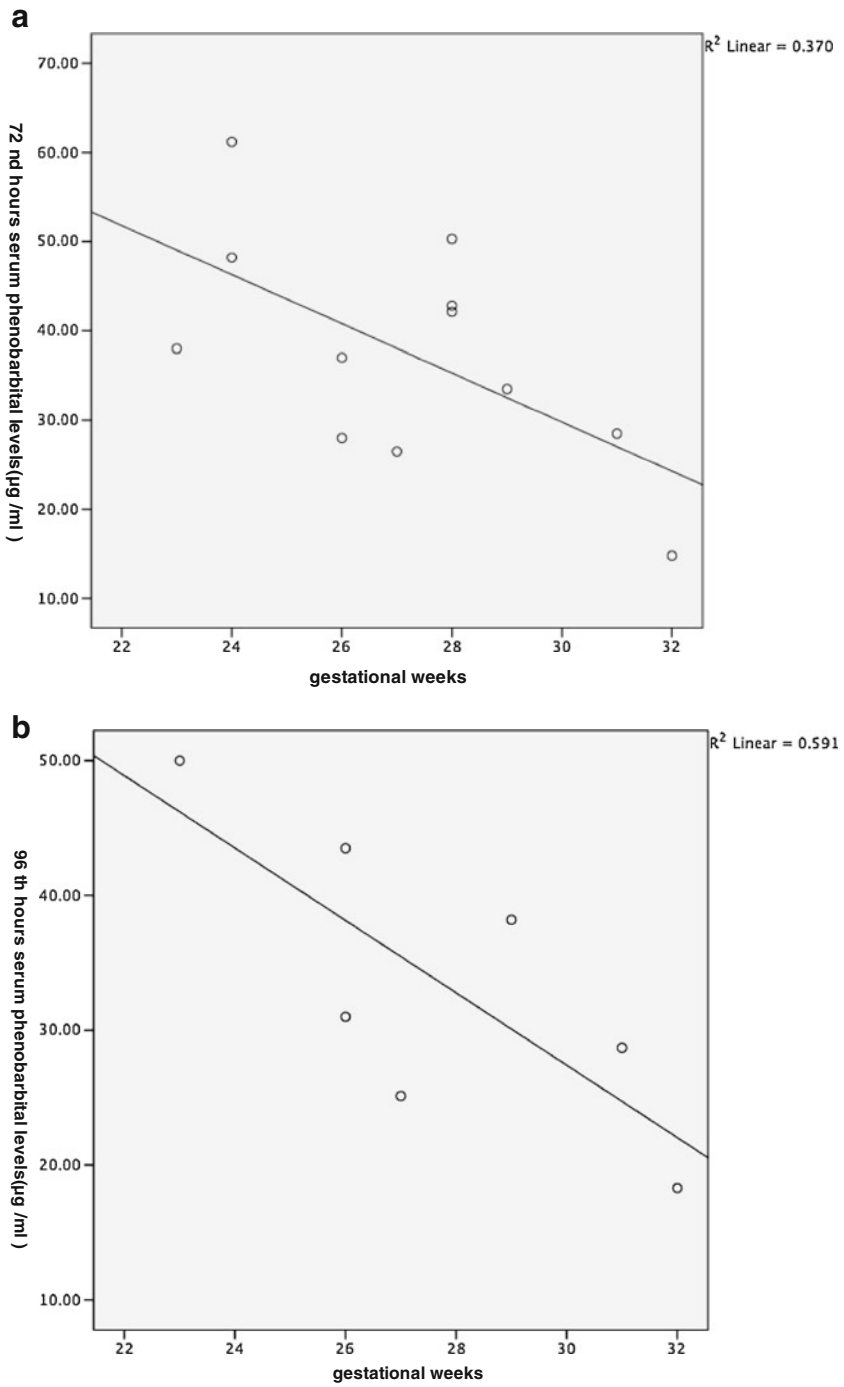

Fig. 1 **a** Correlation between serum concentrations of phenobarbital and the gestational age of infants at the 72th hours. **b** Correlation between serum concentrations of phenobarbital and the gestational age of infants at the 96th hours

drug fractions must be taken into account, in the context of the newborn's systemic illness. Therefore, routine monitoring of free phenobarbital levels is optimal for the management of infants with seizure. The recommended blood levels (15–40 μg/mL) of phenobarbital generally include both the bound and free components in guidelines, and administration doses of this drug are adjusted due to these levels in NICUs [3, 5].

It could not be possible to measure the free fraction of phenobarbital in our laboratory; so, we preferred to exclude patients with serum albumin levels of <2.5 mg/dL and patients taking medicine that is known to bind proteins, in order to eliminate those with higher free phenobarbital concentrations. However, we frequently reached serum concentrations higher than the recommended upper blood limit of phenobarbital, at the 48th hour in 45.8 % and at the 96th hour in 70.8 % of preterms, even the lower recommended dose of phenobarbital (an iv dose of 15 mg/kg as loading and 3 mg/kg/day as maintenance) has been administered.

It is well-known that developmental changes affect the responses to medications and produce a need for age-dependent adjustments in doses. Adjustment of the drug dose for either body weight or body surface area is the most common method used for dosing equations in children and newborns. Developmental differences in pharmacokinetics and pharmacodynamics due to age-dependent changes in body composition are very important [14]. However, Pitlick [15] and Gilman [16] found no correlation between gestational age and phenobarbital elimination half-life or volume of distribution. In contrast, Touw [17] reported in a small group study that phenobarbital pharmacokinetic parameters of Vd, CL tended to decrease with increasing gestational age and height of the neonates.

It is not clear why phenobarbital frequently reaches to blood levels higher than the recommended ranges in VLBW infants. This situation may result either from unidentified pharmacokinetic properties of the drug or from the lower protein binding capacity of phenobarbital in this group of infants. We excluded preterms with albumin levels of 2.5 g/dL; thereby, we tried to eliminate the possibility of lower protein binding capacity. According to our results, a negative correlation was detected between serum concentrations of phenobarbital and the gestational age of infants at the 72th and 96th hours, but not at the 2nd, 24th, and 48th hours. These results might suggest that immaturity is important for the metabolism of phenobarbital. However, it is necessary to investigate the metabolic pathway of phenobarbital in preterms, in order to support this suggestion. In the present study, we did not aim to perform pharmacokinetics study. We just wanted to declare that blood levels of phenobarbital are higher than the reference ranges that those are often reached with the recommended doses in this special group of babies. Therefore, particular attention should be done while administering phenobarbital in preterms.

It was also interesting that we did not detect any side effect of phenobarbital in all of the preterms that had blood levels higher than the recommended ranges. We probably skipped the clinical findings of toxicity (sedation and respiratory depression) as most of the patients have been put on mechanical ventilation. The clinical findings of phenobarbital toxicity (sedation and respiratory depression) might have overlapped with the clinical findings of many diseases in our preterms as intraventricular hemorrhage, sepsis, and metabolic problems.

As far as we know, this is the first pilot study that highlights the safety of phenobarbital loading dose for very small preterm infants even without a very broad study population. Our results suggest that phenobarbital blood levels should be followed closely, as blood levels higher than the reference ranges can often be achieved even in the lower recommended dose of phenobarbital in preterms without specific clinical findings of toxicity. Furthermore, our results demonstrated that it could not be safe for the traditional recommended loading dose of phenobarbital for very low birth weight preterm infants (loading dose of 15 mg/kg and maintenance dose of 3 mg/kg/day). Therefore, we simply suggest that loading dose of phenobarbital for very low birth weight preterm infants might be revised and reinstituted. In this respect, there seems a need for further studies which are good planned, with broad participation, multicenter, and including different loading doses in addition to pharmacokinetic study, in order to reach a consensus on a new recommended dose of phenobarbital for preterm infants with seizures.

References

1. Blume HK, Garrison MM, Christakis DA (2009) Neonatal seizures: treatment and treatment variability in 31 United States Pediatric Hospitals. J Child Neurol 24:148–154
2. Bartha AI, Shen J, Katz KH, Mischel RE, Yap KR, Ivacko JA, Andrews EM, Ferriero DM, Ment LR, Silverstein FS (2007) Neonatal seizures: multicenter variability in current treatment practices. Pediatr Neurol 37:85–90
3. Scher MS (2011) Seizures in neonates. In: Martin RJ, Fanaroff AA, Walsh CH, Walsh MC (eds) Fanaroff and Martin's neonatal-perinatal medicine, 9th edn. Elsevier Mosby, Missouri, pp 976–997
4. Scher MS (2005) Neonatal seizures. In: Taeusch HW, Ballard RA, Gleason CA (eds) Avery's disease of the newborn, 8th edn. Elsevier Saunders 1020, Philadelphia
5. Volpe JJ (2008) Neurology of the newborn, 5th edn. Saunders Elsevier, Philadelphia, pp 231–232
6. Sharpe S, Haas RH (2009) Levetiracetam in the treatment of neonatal seizures. J Pediatr Neurol 7:79–83
7. Ramantani G, Ikonomidou C, Walter B, Rating D, Dinger J (2010) Levetiracetam: safety and efficacy in neonatal seizures. Eur J Pediatr Neurol 3:1–7
8. Fürwentsches A, Bussman C, Ramantani G (2010) Levetiracetam in the treatment of neonatal seizures: a pilot study. Seizure 19:185–189
9. Glass HC, Poulin C, Shevel MI (2011) Topiramate for the treatment of neonatal seizures. Pediatr Neurol 44:439–442
10. Sharpe CM, Capparelli EV, Mower A, Farrell MJ, Soldin SJ, Haas RH (2012) A seven-day study of the pharmacokinetics of intravenous levetiracetam in neonates: marked changes in pharmacokinetics occur during the first week of life. Pediatr Research 72:43–49
11. Glass HC, Kan J, Bonifacio SL, Ferriero DM (2012) Neonatal seizures: treatment practices among term and preterm infants. Pediatr Neurol 46:111–115
12. Nahat MC, Masuoka T, Edwards RC (1988) Developmental aspects of phenobarbital dosage requirements in newborn infants with seizures. J Perinatol 8:318–320
13. Gherpelli JL, Cruz AM, Tsanaclis LM, Costa HP, Garcia TG, Segre CA, Franca AS (1983) Phenobarbital in newborns with neonatal seizures. A study of plasma levels after intravenous administration. Brain Dev 15:258–262
14. Kearns KL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE (2003) Developmental pharmacology, drug disposition action, and therapy in infants and children. N Eng J Med 349:1157–1167
15. Pitlick W, Painter M, Pippenger C (1978) Phenobarbital pharmacokinetics in neonates. Clin Pharmacol Ther 23:346–349
16. Gilman ME, Toback JW, Gal P, Erkan NV (1983) Individualizing phenobarbital dosing in neonates. Clin Pharmacol 2:258–262
17. Touw DJ, Graafland O, Cranendonk A, Vermeulen RJ, Weissenbruch MM (2000) Clinical pharmacokinetics of phenobarbital in neonates. Eur J Pharm Sci 12:111–116