RESEARCH PAPER

Serum Phenobarbitone Levels in Term and Near-Term Neonates with Seizures

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Received: June 10, 2013;
Initial review: October 21, 2014;
Accepted: March 16, 2016.

Objective: To evaluate serum phenobarbitone levels in neonates with seizures and to evaluate the effect of repeated loading dose on serum phenobarbitone levels.

Methods: In this prospective observational study conducted in a tertiary care centre of Northern India during 2011- 2012, 99 neonates admitted with seizureswere included.Serum phenobarbitone levels in neonates with seizures at 20 minutes and 12 hours after the first loading dose of phenobarbitone were measured.

Results: Serum phenobarbitone levels [mean (SD)] at 20 min and 12 hours was 27.3 (28.4) µg/mL and 23 (19.1) µg/mL, respectively (*P*=0.07). The mean serum phenobarbitone levels 12 hours after the loading dose, and proportion of neonates with toxic levels increased with each loading dose of intravenous phenobarbitone.

Conclusion: Monitoring of serum level of phonobarbitone may not be essential because seizure control in neonates appears to be independent of whether serum level is subtherapeutic, therapeutic or toxic range.

Keywords: *Anticonvulsants, Drug Levels, Neonatal convulsions, Toxicity*.

Seizure is the most common neurological emergency in the neonatal period. Most clinical guidelines recommend empirical treatment with phenobarbitone as the first line drug for neonatal seizures [1-3]. While treating seizures, the value of periodic monitoring of plasma levels of phenobarbitone has been recognized on the basis of the known relationship between plasma levels and brain tissue levels [4]. Since phenobarbitone has a narrow therapeutic index and wide inter-patient variability in its utilization, there have been concerns about the dosing schedule [5,6]. The distribution, metabolism and excretion of phenobarbitone may show variability, depending upon the ethnicity, seizure etiology and condition of various body organs [5,7,8]. There is a paucity of studies reporting phenobarbitone levels in neonatal seizures from Indian subcontinent. This study was planned to evaluate the serum phenobarbitone levels in neonates with seizures, and to evaluate the effect of repeated loading dose on serum phenobarbitone levels.

METHODS

This was a prospective observational study, conducted in a level II neonatal intensive care unit of a teaching hospital in Northern India between July 2011 to September 2012. This study was initiated after getting approval from the institutional ethics committee.

Study population included neonates with clinically apparent seizures not responding to treatment of hypoglycemia or hypocalcemia and (*i*) weight more than 2 kg; (*ii*) gestation >34 weeks; and (*iii*) post-natal age less than 4 weeks. Neonates with major congenital malformations and those requiring intubation and ventilation at the time of first seizure were excluded from the study.

Accompanying Editorial: Pages 381-82.

Asphyxia was defined as presence of any one of the following: (*i*) Intramural babies: APGAR score less than 3 at 1 minute and arterial pH <7 at the time of admission, (*ii*) Extramural: history of delayed cry >3 mins after birth. Each neonate was enrolled after obtaining written informed consent of the parent. Neonatal seizures were treated with a loading dose of intravenous phenobarbitone in dose of 20 mg/kg administered over a 20 min period at a rate of 1 mg/kg/min. A responder was defined as an infant who remained seizure-free for a period of 24 hours. For persistent seizures, infants received second dose of phenobarbitone, levetiracetam, phenytoin and/or midazolam as required, according to unit policy. Blood samples for analysis of serum phenobarbitone levels were obtained 20 min (*i.e.* soon after the first loading dose and before second dose of anticonvulsant in case of non-responders) and 12 hours

(before giving first maintenance dose) after the completion of loading dose. Serum was separated and stored at –20°C. Samples were analyzed by the CEDIA Phenobarbital II assay (Microgenics, USA), an *in vitro* method intended for the quantification of phenobarbitone in human serum by spectrophotometry. The serum levels were classified as sub-therapeutic (<10 µg/mL), therapeutic (10-40 µg/ mL) and toxic (>40 µg/ mL).

Analysis of continuous data with normal distribution was done by unpaired t test and non-normally distributed data was done by Mann-Whitney test. Mean of various outcomes were compared using unpaired *t*-test. Repeated measure analysis was done for serum phenobarbitone levels at two time points. Categorical data was compared using chi square or Fischer exact test, as applicable. *P* value less than 0.05 was considered significant.

RESULTS

A total of 119 neonates were admitted with seizures, of which 99 were included in the study. Three had hypoglycemic and 5 had hypocalcemic seizures, two refused consent, 9 required ventilatory support at the time of seizure and one had multiple congenital malformations. The mean (SD) serum phenobarbitone level at 20 min and 12 hours was 27.3 (28.4) and 23.0 (19.1) mcg/mL, respectively (*P*=0.07) (***Fig.* 1**). Therapeutic serum levels were attained in only 51 (58%) neonates, while 23 (26%) had sub-therapeutic levels and 14 (16%) had toxic levels of serum phenobarbitone at 12 hours. Clinical control of seizure after single loading dose of 20 mg/kg was achieved in 44 (44.4%) neonates. Proportion of seizure control in neonates with serum phenobarbitone level in therapeutic, sub-therapeutic and toxic range was 22 (46%), 8 (40%) and 8 (47%), respectively (*P*=0.8). Time to reach full enteral feed and oral feed was comparable in neonates achieving therapeutic, sub-therapeutic and toxic levels of serum phenobarbitone. In neonates with hypoxic ischemic encephalopathy (HIE), though the mean serum level at 20 min was higher in HIE stage 3 than stage 1 or stage 2, the difference in serum levels in the three stages was not significant (*P*=0.42). The mean serum phenobarbitone levels 12 hours after the loading dose, and proportion of neonates with toxic levels increased with each loading dose of intravenous phenobarbitone (***Table* I**).

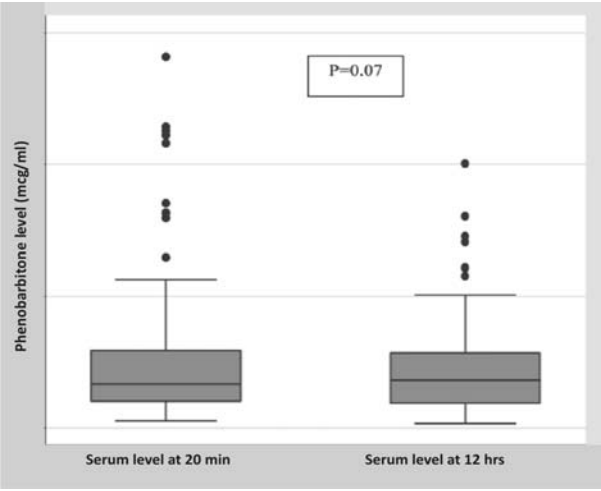

FIG. 1 *Box and Whiskers plot for serum phenobarbitone levels.*

DISCUSSION

Our study demonstrated that seizure control in neonates was not different in those with subtherapeutic, therapeutic or toxic levels of phenobarbitone. We also found that serum phenobarbitone level after first loading dose of intravenous phenobarbitone was within therapeutic range in only about 60% of babies.

In our study, clinical control of seizures occurred in only 44.4% of neonates which was similar to some earlier studies [9,10]. In a previous study at our center, we found a high response rate of 72% in the phenobarbitone group; however, serum levels were not analyzed [11]. Few studies have attempted to correlate serum phenobarbitone levels with control of neonatal seizures. Jamie, *et al*. [10] reported a direct relationship between serum concentration and response to phenobarbitone. In our study, though the mean serum level was slightly higher in the seizure control group as compared to group in which seizures were not controlled, the difference was not statistically significant. Jalling, *et al*. [12] reported that convulsion ceased at serum levels between 12 and 30 mcg/mL, although there was a subgroup of convulsing patients whose seizures could not be controlled despite achievement of therapeutic levels. In our study, the minimum serum phenobarbitone level at which seizure was controlled was 6 mcg/mL. Ouvrier and Goldsmith [13] have also documented seizure control with phenobarbitone levels in range of 7 to 15 mcg/mL.

There were some neonates with unexpectedly high or low serum levels documented in our study. This variance in

TABLE I SERUM PHENOBARBITONE LEVELS ACCORDING TO LOADING DOSE GIVEN

	Loading dose		
	20 mg/kg (n = 44)	*30 mg/kg (n = 29)*	*40 mg/kg (n=6)*
Level at 12 hours (µg/mL); Mean (SD)	19.3 (17)	25.3 (16.3)	48.9 (31.7)
*Neonates with toxic levels at 12 h, *n* (%)	4 (9)	5 (17)	4 (66)

**P=0.003 for number with toxic levels in 40 mg/kg vs 20 mg/kg group.*

WHAT THIS STUDY ADDS?

- Repeated doses of phenobarbitone can lead to toxic levels in neonates when given in widely recommended doses of up to 40 mg/kg.

serum level could also be due to the heterogeneity of post-natal age and etiology of seizures, both of which have been reported to unpredictably affect serum levels in earlier studies [5,7]. Researchers have documented more than 50% reduction in clearance of phenobarbitone in asphyxiated neonates, compared to non-asphyxiated neonates, leading to higher serum levels in the former [10,14]. This was in contrast to a study by Fischer, *et al.* [15], who demonstrated lower levels in neonates with asphyxia, probably due to the effect of chronic hypoxia, which may promote the metabolism of phenobarbitone. In our study, we did not find any association of asphyxia and serum levels.

Our study demonstrated that with each subsequent loading dose of phenobarbitone after 20 mg/kg results in significant increase in the number of neonates attaining toxic levels. Therefore, alternative or second line drugs should probably be used, rather than the repeated doses of phenobarbitone in neonates not responding to first loading dose of phenobarbitone, especially if facility to monitor serum levels are not there at the center of treatment. However, further studies with more patients receiving multiple loading doses of phenobarbitone are required.

A limitation of our study was that continuous EEG monitoring was not done and abolition of electrical seizures could not be documented.

We conclude that intravenous loading dose of phenobarbitone at 20 mg/kg results in therapeutic levels in most neonates, but both sub-therapeutic and toxic levels of phenobarbitone are possible. Seizure control appears to be independent of whether serum level is subtherapeutic, therapeutic or toxic range.

Contributors: SW: collected and compiled the data for the study, and drafted the initial manuscript; AU: conceptualized and designed the study, analyzed the data and finalized the manuscript. He shall act as guarantor of paper. NC: performed the serum phenobarbitone levels ; MR, PS: helped in collecting blood samples, data and preparation of manuscript.

Funding: Partially funded by 'Thesis/ Research grant' of Indian Council for Medical Research (ICMR), New Delhi, India.
Competing interest: None stated.

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