

Dose de Fenobarbital Durante a Hipotermia Induzida - Deveremos Mudar a Nossa Prática?

Phenobarbital Dosing During Therapeutic Hypothermia - Should We Change Our Practice?

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Introdução: O fenobarbital é um fármaco anticonvulsivante de primeira linha nas convulsões neonatais. No entanto, durante o tratamento com hipotermia induzida, têm vindo a ser levantadas preocupações com os níveis séricos obtidos devido a alterações na farmacocinética. O objetivo do presente estudo foi a avaliação dos níveis de fenobarbital em recém-nascidos tratados com hipotermia após terem sido tratados com doses diferentes de fenobarbital na sequência das necessidades individuais e de protocolos de atuação diversos conforme o hospital de origem.

Métodos: Foram estudados recém-nascidos tratados com hipotermia induzida e que receberam fenobarbital no primeiro dia de vida. Os doentes foram divididos em dois grupos de acordo com a dose total recebida (≤ 20 mg/kg ou >20 mg/kg) e foram analisados os níveis séricos em intervalos consecutivos após a última administração (12-24 horas, 24-48 horas, 48-72 horas e mais de 72 horas).

Resultados: Foram estudados 31 doentes, sendo a mediana da dose de fenobarbital de 20 mg/kg. Foram encontradas diferenças significativas entre os grupos em todos os intervalos de tempo estudados. Os doentes que receberam doses ≤ 20 mg/kg apresentaram níveis terapêuticos em todos os períodos e nunca atingiram níveis tóxicos. Por outro lado, foram encontrados níveis tóxicos numa proporção significativa de doentes que receberam doses totais > 20 mg/kg.

Discussão: Existe um risco significativo de níveis tóxicos de fenobarbital após administração de doses > 20 mg/kg em doentes tratados com hipotermia induzida. Nestes doentes, os níveis séricos de fenobarbital devem sempre ser avaliados após uma dose total de 20 mg/kg e o uso de anticonvulsivantes alternativos deve ser considerado se o controlo das crises não for alcançado, a menos que os níveis de fenobarbital sejam subterapêuticos.

Palavras-chave: Fenobarbital/uso terapêutico; Hipotermia Induzida; Hipóxia-Isquémia, Cérebro; Monitorização de Medicamentos; Recém-Nascido

Abstract

Introduction: Phenobarbital is a first-line anticonvulsant for neonatal seizures. However, during therapeutic hypothermia, there are concerns about its levels due to changes in drug metabolism. We aimed to study phenobarbital levels in newborns treated with hypothermia after receiving different phenobarbital dosing schedules according to different protocols at referring hospitals and to patients' needs.

Methods: We studied patients undergoing therapeutic hypothermia who were treated with phenobarbital during the first day of life. Patients were divided into two groups according to the total dose received (≤ 20 mg/kg or > 20 mg/kg) and phenobarbital levels attained were analysed in consecutive time periods after the last dose (12-24 hours, 24-48 hours, 48-72 hours and over 72 hours).

Results: We studied 31 infants. The median phenobarbital dose was 20 mg/kg. Significant differences were found between groups at all the time periods studied. Infants receiving ≤ 20 mg/kg had therapeutic levels in all time

periods, never approaching toxic levels. However, toxic levels were found in a significant proportion of patients receiving a total dose >20 mg/kg.

Discussion: We found a significant risk of toxic levels with phenobarbital doses >20 mg/kg in cooled infants. In these infants, serum phenobarbital levels should always be measured after a total dose of 20 mg/kg and alternative anticonvulsant drugs should be considered if seizure control is not achieved, unless phenobarbital levels are below the therapeutic range.

Keywords: Drug Monitoring; Hypothermia, Induced; Hypoxia-Ischaemia, Brain; Infant, Newborn; Phenobarbital/therapeutic use

Introduction

Phenobarbital is a first-line anticonvulsant for neonatal seizures,¹ including during therapeutic hypothermia (TH) in the context of hypoxic-ischaemic encephalopa-

thy (HIE). The most commonly used initial dose is 20 mg/kg and further 5 mg/kg doses are given to achieve seizure control, up to a maximum dose of 40 mg/kg. Optimal phenobarbital levels to achieve seizure control are above 15 µg/mL, but the upper limit accepted as a toxic level varies between 30 and 40 µg/mL in different studies²⁻⁴ and units' protocols.

Phenobarbital toxicity in the developing brain is a matter of debate between scientists, and conflicting pre-clinical⁵ and clinical⁶ results have been published, some of them indicating that phenobarbital in HIE patients treated with TH is potentially unsafe.⁶ We are not aware of any randomised controlled trials addressing this issue, but we can speculate that, if there is any risk associated with phenobarbital use in HIE infants treated with TH, this risk can be considerably increased if toxic levels are attained.

Hypothermia is associated with physiological changes to many organ systems, including the liver and kidney, and modifies the pharmacokinetics of various drugs, including phenobarbital.⁷ Phenobarbital is metabolised by cytochrome P450, the activity of which is also known to be affected by hypothermia,⁸ though some authors report that the pharmacokinetics of phenobarbital is not significantly changed by TH.^{9,10} Nevertheless, despite some concern expressed about the use of conventional dosing schemes, which could lead to toxic phenobarbital levels in asphyxiated infants,¹¹ especially when undergoing TH,¹² we are not aware of any change in the dosing recommendations for phenobarbital in patients treated with hypothermia. Some authors have described similar phenobarbital pharmacokinetics between infants with HIE treated and not treated with hypothermia, further supporting the use of conventional dosing schemes.^{9,10}

Our neonatal intensive care unit (NICU) introduced TH in Portugal in 2010,¹³ adopting a protocol that was based on *Total Body Hypothermia for Neonatal Encephalopathy Trial (TOBY)*.¹⁴ In accordance with the international guidelines,¹⁵ we implemented a close monitoring system for clinical variables, including phenobarbital levels. Since most of our treated patients are outborn and we have a hospital-independent neonatal transport system, we are unable to control phenobarbital dosing schemes given before arrival at our NICU, either at places of birth or during transport, and we found that different dosing schemes were used. We also detected phenobarbital levels above the therapeutic range in some patients, further increasing our concern that conventional dosing schedules may need some adjustment to avoid toxic levels. In this study, we aimed to study phenobarbital levels in newborns treated with hypothermia after receiving different initial phenobarbital dosing schemes

in order to confirm our empirical impression that typical dosing schemes may be dangerous in this context.

Methods

We retrospectively analysed data from patients undergoing TH in our NICU during a three-year period (2010-2012). All patients who received phenobarbital during the first 24 hours of life were included.

Due to lack of uniform guidelines on phenobarbital doses given at the original hospital or during transport, patients were treated with different dosing schemes before arriving to our NICU. Patients were then divided into two groups according to the total dose received during the first 24 hours of life: (A) ≤ 20 mg/kg; (B) > 20 mg/kg. At our unit we do not routinely give maintenance doses of phenobarbital during hypothermia in most cases due to concerns about increasing the risk of attaining toxic levels due to accumulation of the drug. Clinical data were extracted from our prospectively collected institutional hypothermia registry. Serum phenobarbital levels for all treated patients were retrieved from our institutional laboratory database and assessed in four consecutive time periods: 1) 12-24 hours; 2) 24-48 hours; 3) 48-72 hours; 4) >72 hours. When additional doses were given after 24 hours of life, subsequent levels were not considered.

Phenobarbital levels were measured by particle-enhanced turbidimetric inhibition immunoassay (PETINIA) (method accuracy 1 µg/mL, range of measurement 0-80 µg/mL). Therapeutic phenobarbital levels were considered to be 15-30 µg/mL, near-toxic levels 30-40 µg/mL and toxic levels above 40 µg/mL.

Our study was not set out to evaluate seizure control, but seizure control was ultimately obtained in all patients with a protocol consisting of phenobarbital, midazolam and lidocaine (used very rarely). Specific toxic effects of phenobarbital are very difficult to assess in these patients, since most described effects are not easily distinguished from the effects of HIE itself, hypothermia or other drugs used for treatment of HIE, and thus will not be reported in this paper.

Statistical analysis of numerical variables was performed using the independent-sample t test or the Mann-Whitney test after checking for normality of the sample distribution with the Shapiro-Wilk test. Statistical analysis of categorical variables was performed with Chi-squared tests. IBM SPSS 21® software was used for analysis.

Results

During the study period 37 patients underwent TH at our NICU, of whom 34 were outborn. We evaluated 31 patients (84%) who received phenobarbital at a median dose of 20 mg/kg during the first 24 hours of life due to seizures or suspected seizures. Most patients (61%) received total doses of 20 mg/kg or less (minimum dose received 10 mg/kg, mean dose received 16.8 mg) (group A), but a significant percentage (39%) received a total dose above 20 mg/kg (maximum dose received 40 mg/kg, mean dose received 30 mg/kg) (group B). The distribution of total doses is depicted in Fig. 1. Five patients received additional doses of phenobarbital, one during the first 12 hours and four between 48 and 72 hours, but levels obtained after these additional doses were not considered for the statistical analysis.

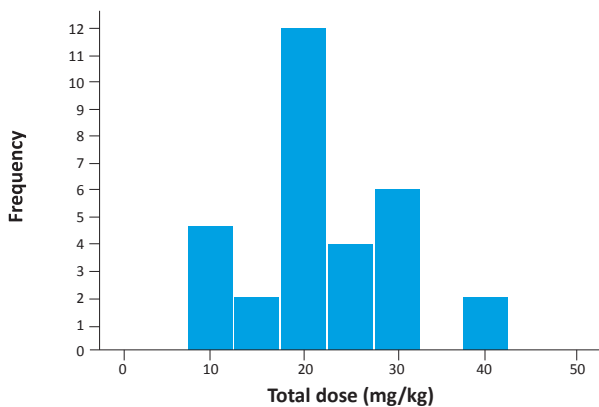
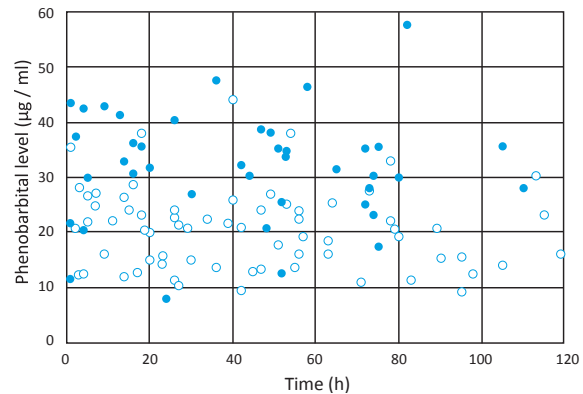


Figure 1. Distribution of total doses phenobarbital given during the first 24 hours of life.

There were no significant differences between the groups regarding initial pH (6.99 vs 6.98), base deficit (16.9 vs 18.7), 10 minute Apgar score (5 vs 5), or admission temperature (33.1 °C vs 33.3 °C). Infants in group B more often had severe encephalopathy (21% vs 58%, $p < 0.05$) and higher Thompson scores at 24 hours (11 vs 14, $p < 0.05$), but not on admission or after 24 hours. Passive hypothermia was achieved at a median of one hour of life and active cooling was started at a median of six hours of life. Rates of hypotension during treatment (57% vs 64%), acute renal failure (16% vs 17%) and coagulation disturbances (28% vs 28%) were not statistically different between the groups.

Phenobarbital levels were measured at four consecutive time periods with mean intervals after the last dose of: 1) 17.4 hours; 2) 35.5 hours; 3) 55.7 hours; 4) 87.8 hours. Ninety-seven percent of patients contributed to the study with phenobarbital levels at two or more time periods and 70% contributed with three or more. Individual dose-interval values according to study groups are depicted in Fig. 2.

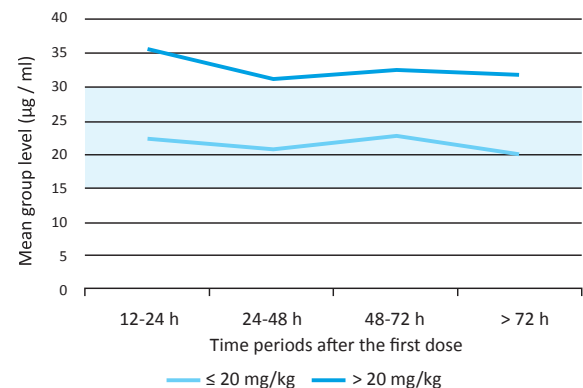


Open circles: ≤ 20 mg/kg; filled circles: > 20 mg/kg.

Figure 2. Individual phenobarbital levels at different time intervals after administration, according to total dose administered.

Individually, most phenobarbital levels of patients who received total doses above 20 mg/kg had levels above 30 µg/mL at all time periods and levels above 40 µg/mL were identified on seven occasions (Fig. 2). By contrast, the great majority of patients receiving 20 mg/kg or less had levels within the therapeutic range.

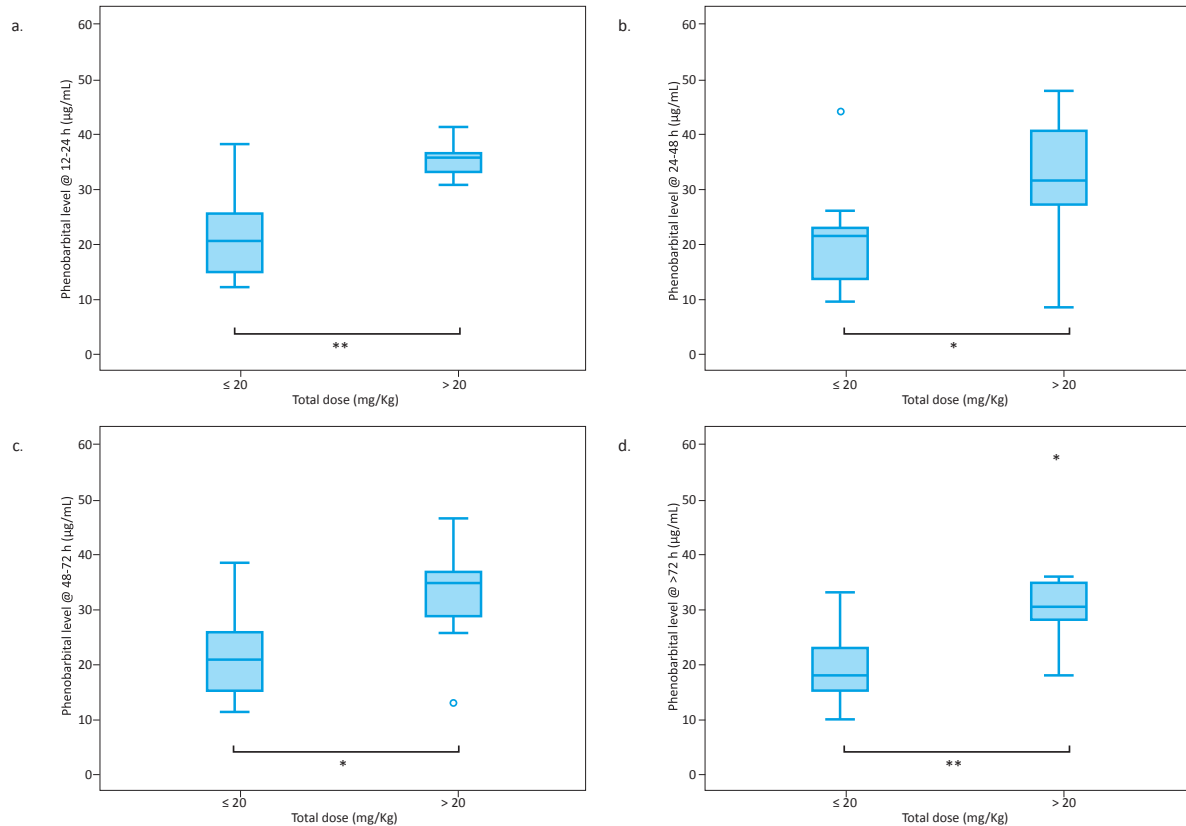
When we examined the distribution of mean phenobarbital levels across the groups at different time periods, we found that mean levels for infants in group B were in the near-toxic range in all time periods (Fig. 3).



Recommended therapeutic range (15-30 µg/mL) shown in light blue.

Figure 3. Progression of mean serum levels of phenobarbital according to cumulative dose administered during the first 24 hours.

Analysis of the distribution of phenobarbital levels for each time period showed that most infants in group A had levels within the therapeutic range, whereas more than half of infants in group B had levels in the near-toxic or toxic range (Figs. 2 and 4). Also, when analysing group differences for all time periods, we found significant differences between groups A and B for all the four time periods studied and these differences were more significant between 12-24 hours of life and after 72 hours of life (Figs. 4a and 4d).



Recommended therapeutic range (15-30 µg/mL) shown in light blue area.

Significant differences were found for levels obtained at all time periods (* $p < 0.05$; ** $p < 0.001$).

Figure 4. Distribution of phenobarbital levels at different time periods (12-24 hours, 24-48 hours, 48-72 hours and after 72 hours) after administration of a cumulative dose, according to the total dose administered.

Discussion

Our data show that there was a significant risk of toxic levels when total phenobarbital doses above 20 mg/kg were used in this group of patients treated with TH. This finding can be explained by delayed clearance of phenobarbital, which can be partially attributed to hypothermia.^{8,12}

Most infants with HIE can be successfully treated with relatively modest doses of phenobarbital, leaving us with no more than anecdotal evidence of toxic phenobarbital levels in newborns treated with TH.¹² The absence of a significant pool of newborns treated with TH and higher dosages of phenobarbital probably underlies the lack of sufficiently strong evidence to lead to a change in dosing recommendations. Nevertheless, 39% of our sample received a total dose above 20 mg/kg, allowing us to draw some additional conclusions on this issue.

We did not set out to perform a formal pharmacokinetic study, but only to confirm our clinical impression that babies receiving extra doses of phenobarbital for seizure

control had an increased risk of attaining near-toxic or toxic drug levels, despite the absence of maintenance doses in our NICU's protocol.

The theoretical risk of altered phenobarbital metabolism in newborns treated with TH for HIE,^{7,8} added to the potential risk of phenobarbital per se,⁶ and to reports that confirm important changes in phenobarbital half-life in this setting,¹² should, in our view, be addressed carefully.

The attainment of therapeutic levels in our sample with total doses up to 20 mg/kg and the risk of near-toxic or toxic levels when a total dose of 20 mg/kg is exceeded suggest that the contribution of phenobarbital to seizure control in the setting of TH can be safely attained with lower doses. Although not shown, we separately compared dosages below 20 mg/kg with dosages equal to 20 mg/kg and no significant differences in mean levels were observed between those two subgroups. Most infants who were given total doses below 20 mg/kg (10 mg/kg in five and 15 mg/kg in two infants) attained therapeutic levels and had seizure control.

Given the considerable risks of phenobarbital-induced

apoptosis,¹⁶ particularly in these infants with increased risk of long-term neurodevelopmental sequelae, and given the easy attainment of therapeutic levels with total doses of phenobarbital up to 20 mg/kg in our study, we speculate that using an initial dose of 10 mg/kg followed by additional doses of 5 mg/kg up to a total dose of 20 mg/kg may be a safer protocol in infants undergoing TH. In these infants, serum phenobarbital levels should always be measured after a total dose of 20 mg/kg and alternative anticonvulsant drugs should be considered if seizure control is not achieved, unless phenobarbital levels are below the therapeutic range.

O QUE ESTE ESTUDO TRAZ DE NOVO

- Existe uma grande diversidade de esquemas posológicos para o fenobarbital no contexto de encefalopatia hipoxico-isquêmica perinatal.
- A utilização de esquemas com dose total superior a 20 mg/kg associa-se a um risco significativo de níveis tóxicos.
- Antes de se obter um nível sérico, desaconselha-se a utilização de doses totais acima de 20 mg/kg, devendo-se optar por anticonvulsivantes alternativos.

Conflitos de Interesse

Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento

Não existiram fontes externas de financiamento para a realização deste artigo.

Proteção de Pessoas e Animais

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

Confidencialidade dos Dados

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.

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