ELSEVIER

Brain & Development xxx (2018) xxx–xxx

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

High dose phenobarbitone coma in pediatric refractory status epilepticus; a retrospective case record analysis, a proposed protocol and review of literature

Sheffali Gulati [a,*], Vishal Sondhi [a], Biswaroop Chakrabarty [a], Prashant Jauhari [a], Rakesh Lodha [b], Jhuma Sankar [b]

[a] *Child Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India*
[b] *Division of Pulmonology and Intensive Care, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India*

Received 18 September 2017; received in revised form 5 November 2017; accepted 25 November 2017

Abstract

Background: Ongoing refractory status epilepticus is associated with significant morbidity and mortality. Therapeutic coma induction with midazolam, thiopentone, phenobarbitone or propofol is indicated when conventional antiepileptics fail to abort seizure. Of these, the most extensively studied is midazolam. Amongst the remaining three, phenobarbitone has the most favourable pharmacological profile, but has not been studied adequately, more so in the pediatric age group. The current retrospective case records analysis is an attempt to describe use of phenobarbitone coma in pediatric refractory status epilepticus.

Methods: Case records of patients, admitted with status epilepticus to the pediatric inpatient services of a tertiary care teaching hospital of North India between January 2014 and December 2016 were reviewed. Those with refractory status epilepticus who failed to respond to midaolam infusion and phenobarbitone coma was used were included for analysis.

Results: Overall, 108 children presented in status, of which 34 developed refractory status epilepticus. Of these 34, 21 responded to midazolam infusion and in 13 high dose phenobarbitone coma following a standardised protocol was used. Amongst these 13 (8 males and 5 females, median age 6 years, IQR: 2.5–9.5), 12 responded and 1 succumbed. The median time to clinical seizure resolution and desired electroencephalographic changes post phenobarbitone initiation were 16 (IQR: 12–25) and 72 h (IQR: 48–120) respectively.

Conclusion: High dose phenobarbitone appears to be an effective therapeutic modality in pediatric refractory status epilepticus. The current study provides a protocol for its use which can be validated in future studies with larger sample size.

Keywords: High dose phenobarbitone; Refractory status epilepticus; Pediatric; Protocol

1. Introduction

Status epilepticus (SE) is a medical emergency and the care involves concurrently administering drugs to terminate the ongoing seizures and identification of underlying etiology. The operational definition for convulsive SE is "≥5 min of continuous seizure or two or more discrete seizures between which there is incomplete recovery of consciousness" [1,2].

Most commonly benzodiazepines are used as the first line anti-epileptic drug (AED) with nearly 65% success rate [3]. This is followed by phenytoin/fosphenytoin as second line therapy. The children who continue to have

* Corresponding author at: Child Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110029, India.
E-mail address: sheffalig@yahoo.com (S. Gulati).

https://doi.org/10.1016/j.braindev.2017.11.009
0387-7604/

seizures despite treatment with adequate doses of benzodiazepine and one AED constitute refractory status epilepticus (RSE). Systemic changes that begin during SE, worsen during RSE and include impairment of cerebral perfusion (brain hypoxia, hypoglycemia, acidosis), hyperthermia, rhabdomyolysis and related renal failure, stress cardiomyopathy and, rarely, neurogenic pulmonary edema [4]. These significantly contribute to morbidity and mortality associated with RSE. Thus, it imperative to achieve an emergent control of ongoing seizures.

The treatment of RSE has not been analyzed in a randomized trial and the literature gives a spectrum of treatment options with variable end-points. Most published literature list the use of midazolam, pentobarbitone/phenobarbitone or propofol infusions to induce coma; however, the treatment practices for same are largely anecdotal. Abend et al. in 2008 suggested a protocol for management of SE and RSE with suggestions for induction of coma with midazolam, but there is no guideline for management of RSE after the failure of midazolam infusion [5]. The protocol by Abend et al. was modified and adopted at the current centre, incorporating guidelines for induction of high dose phenobarbitone (HD-PHB) coma. This aim of this study was to investigate the clinical and electrographic response of pediatric patients with midazolam resistant RSE that were managed with HD-PHB coma according to a standardized protocol.

2. Methods

2.1. Patients

The pool of possible cases, was identified after reviewing the record of patients admitted with SE, to the pediatric inpatient care at a tertiary care teaching centre in North India between January 2014 and December 2016. The medical records of all identified patients were retrieved and RSE was defined as SE resistant to benzodiazepines and one-second line agent, viz., phenytoin/valproate/phenobarbitone/levetiracetam [6–8]. The patients who had received phenobarbitone in accordance with the standardized institutional protocol were included for analysis. The baseline demographic details and information about the underlying diseases, precipitant for SE, clinical and biochemical profile and outcome were chronicled.

Approval to do this retrospective case record analysis was obtained from Institute Ethics Committee. All the patients were coming for regular follow up in the Outpatients and informed consent was obtained from parents and/or caregivers to use their clinical details for medical publication without disclosing the identity of patients. One patient who died, informed consent was obtained telephonically. In the current centre, phenobarbitone coma is part of routine clinical management of pediatric status epilepticus refractory to midazolam infusion. Consequently, in all patients before starting it, the benefits and adverse effects are discussed with parents and/or caregivers.

2.2. Protocol for management of status epilepticus and refractory status epilepticus

2.3. Management of SE

The protocol suggested by Abend et al. [5], was modified and adapted for management of SE and RSE. Any child presenting to the hospital with on-going convulsive seizure was administered intravenous benzodiazepine (Lorazepam = 0.1 mg/kg, Midazolam = 0.2 mg/kg, Diazepam = 0.2 mg/kg). If the seizure did not terminate within 5 min of benzodiazepine administration, then a repeat dose of benzodiazepine was given. Concurrently, with the second dose of benzodiazepine, the anti-epileptic naive patients were loaded with intravenous phenytoin (20 mg/kg infusion over 20–30 min). In patients who had presented with SE following poor compliance to AEDs, a loading dose of missed AED was administered (Phenytoin = 10 mg/kg, Valproate = 10 mg/kg, Levetiracetam = 10 mg/kg, Phenobarbitone = 10 mg/kg).

2.4. Management of RSE

If the seizures persisted 10 min after completion of phenytoin (or alternative AED) infusion, then the patient was diagnosed to have RSE. Thereafter, the patient was administered intravenous valproate at 20 mg/kg over 20 min. If he/she has already received valproate or valproate is contra-indicated, then intravenous levetiracetam was administered at 20 mg/kg over 20 min. If seizures persisted 5 min after valproate or levetiracetam infusion, then intravenous phenobarbitone was administered at 20 mg/kg over 15 min.

2.4.1. Midazolam coma induction

If seizures persisted 10 min after phenobarbitone infusion, then coma induction was initiated with midazolam infusion. This involved initial bolus of midazolam at 0.2 mg/kg over 2 min followed by infusion at 5 μg/kg/min (~0.3 mg/kg/hour). If seizure persisted 5 min after midazolam bolus, then repeat bolus of midazolam 0.2 mg/kg was administered and infusion rate was increased by 2–3 μg/kg/min. These steps were repeated to a maximum midazolam infusion rate of 15–20 μg/kg/min. During midazolam infusion, the child underwent EEG at least every 12 h.

2.4.2. HD-PHB protocol

If a child continued to have convulsive seizures or non-convulsive electrical status epilepticus despite

Please cite this article in press as: Gulati S et al. High dose phenobarbitone coma in pediatric refractory status epilepticus; a retrospective case record analysis, a proposed protocol and review of literature. Brain Dev (2018), https://doi.org/10.1016/j.braindev.2017.11.009