

Original article

Efficacy and tolerability of high-dose phenobarbital in children with focal seizures

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Abstract

Objective: We retrospectively reviewed the outcomes of children with focal epilepsy treated with oral high-dose phenobarbital.

Methods: We reviewed data on children (aged < 15 years) with focal seizures treated with high-dose phenobarbital (>5 mg/kg/day to maintain a target serum level >40 µg/mL) for at least 6 months. Seizure frequency was evaluated after phenobarbital titration, and 1 and 2 years after high-dose phenobarbital treatment commenced. Treatment was judged effective when seizure frequencies fell by ≥75%.

Results: Seven boys and eight girls were treated. The median age at commencement of high-dose phenobarbital therapy was 30 months. The maximal serum phenobarbital level ranged from 36.5 to 62.9 µg/mL. High-dose PB was effective in seven. In two patients, treatment was transiently effective, but seizure frequency later returned to the baseline. High-dose PB was ineffective in six. No significant association between effectiveness and any clinical variable was evident. Drowsiness was recorded in nine patients, but no patient developed a behavioral problem or hypersensitivity.

Conclusion: Oral high-dose phenobarbital was effective in 7 of 15 patients with focal epilepsy and well tolerated. High-dose PB may be useful when surgical treatment is difficult.

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Keywords: Phenobarbital; Efficacy; Tolerability; Serum level

1. Introduction

Phenobarbital (PB) has been used as an antiepileptic drug (AED) for over 100 years. PB revolutionized epilepsy treatment and continues to be prescribed worldwide today. PB effectively treats both focal and

generalized seizures. PB is on the essential drug list of the World Health Organization: “Monotherapy with any of the standard AEDs (carbamazepine, PB, phenytoin, and valproic acid) should be offered to children and adults with convulsive epilepsy” [1]. In the NICE guidelines, PB is included in the AEDs that may be considered to treat focal seizures upon referral to tertiary care [2]. However, the use of PB is decreasing, because many excellent AEDs including carbamazepine, phenytoin, and valproate have subsequently been developed and applied.

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Several authors have reported that high-dose PB effectively treated refractory status epilepticus [3–5]. In these studies, PB was given intravenously. Moreover, a few reports claimed that oral or rectal high-dose PB effectively treated refractory epilepsies [6,7]. However, only short-term data were presented. We thus retrospectively reviewed the outcomes of children with focal epilepsy, treated with high-dose PB for >6 months, to explore drug efficacy and tolerability.

2. Patients and methods

We retrospectively reviewed data on children (age < 15 years) with focal seizures treated with high-dose PB for at least 6 months between April 2009 and March 2012 at the Department of Pediatrics, Juntendo University Hospital. High-dose PB was defined as a PB dose >5 mg/kg/day used to attain a target serum PB level >40 µg/mL. The initial dose of PB was 0.5–2 mg/kg/day and this was increased by 0.5–2 mg/kg/day every 2–4 weeks to attain the required serum level. PB was administered orally to most patients, but was given intravenously to some patients when rapid titration was necessary. We considered high-dose PB for children with focal seizures for the following reasons. In ten patients, their seizures were refractory to several other AEDs. In the other five patients, severe seizure clusters or status epilepticus occurred and their seizures were controlled by intravenous PB. Maintenance with oral high-dose PB was chosen as chronic treatment before trying to substitute PB into some other AED. Surgeries such as lesionectomy and hemispherectomy were considered to be too difficult in all children for at least one of the following reasons; severe neurological handicap which was unlikely to be improved by surgery, widespread brain lesions, genetic etiology including chromosomal aberration, and difficulty in determining seizure focus. The study was approved by the institutional review board of the Juntendo University Faculty of Medicine.

We collected the following data from medical records: sex, underlying disorders, age at the onset of epilepsy, extent of psychomotor development, AEDs that had been used before high-dose PB, age at initiation of high-dose PB, and the maximal dose of PB given. Seizure frequency was assessed at the initiation of high-dose PB, after titration of high-dose PB, and 1 and 2 years after high-dose PB was commenced. Peak serum PB levels were measured 1–3 times per year. The ictal foci of seizures could not be determined; ictal EEG recordings were lacking for most patients.

The efficacy of high-dose PB was categorized as follows: seizure-free or $\geq 75\%$ reduction in seizure frequency (effective); $\geq 75\%$ reduction for at least 6 months followed by a return to the baseline seizure

frequency (transiently effective); or <75% reduction, or an increase, in seizure frequency (ineffective). Adverse events were noted at every hospital visit.

The levels of several clinical variables were compared by treatment efficacy using Fisher's exact probability test to examine categorical variables and the Mann–Whitney *U*-test to explore continuous variables. Patients in whom the drug was transiently effective or ineffective were grouped into an 'ineffective' group, and the others into an 'effective' group. Maximal serum PB levels were compared between those with and without drowsiness. All statistical analyses were performed with the aid of SPSS version 17.0 (SPSS, Tokyo, Japan). Statistical significance was accepted when the *p* level was <0.05.

3. Results

The results are summarized in Table 1.

We identified 15 patients (7 boys and 8 girls) with focal seizures treated with high-dose PB for >6 months. The median age at the onset of epilepsy was 8 months (range: 0.3–93 months). The etiology of epilepsy was acute encephalopathy in four, neonatal hypoxic-ischemic encephalopathy in two, chromosomal aberrations in two, lissencephaly in one, tuberous sclerosis in one, periventricular leukomalacia in one, and unknown in four. All patients exhibited delayed psychomotor development, which was severe in 12. The median number of antiepileptic drugs taken before high-dose PB treatment was one (range: 0–6).

The median age at initiation of high-dose PB treatment was 30 months (range: 1–94 months). The maximal dose of PB ranged from 8.2 to 29.6 mg/kg/day (median: 10.5 mg/kg/day). The maximal serum PB levels ranged from 36.5 to 62.9 µg/mL (median: 47.9 µg/mL). Twelve of the 15 patients were suffering multiple daily seizures when high-dose PB was commenced. After drug titration, seizure frequency was reduced by $\geq 75\%$ in eight patients (Nos. 1, 4, 6, 7, 10, 11, 13, and 15). Patients 1, 7, and 13 became seizure-free. PB was discontinued within 12 months after titration in 4 patients (Nos. 2, 5, 9, and 12) because of lack of efficacy. Two years after initiation of high-dose PB, the regimen remained effective in six patients (Nos. 4, 6, 7, 11, 13, and 15), whereas seizure frequency returned to baseline levels in patients 1 and 10. In patient 8, seizure frequency was not reduced in the first year of drug treatment, but was thereafter. Eventually after two-year follow-up, high-dose PB was effective in seven patients, transiently effective in two, and ineffective in six.

For the comparison of patients' characteristics according to the efficacy, patients in whom the drug was transiently effective or ineffective were grouped into an 'ineffective' group, and the others into an 'effective' group. Children in whom the drug was effective and was ineffective did not differ significantly with respect

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