Phenytoin administration in the newborn and infant

Federico Sicca, Annarita Contaldo, Elisabeth Rey, Olivier Dulac

Abstract

To evaluate the efficacy and safety of phenytoin (PHT) in the treatment of situation-related seizures and epilepsies in the newborn and infant; the clinical histories of 82 patients were retrospectively reviewed. Sixty patients received for status epilepticus (SE), intravenous PHT followed by long-term oral administration for 27 of them. The other 22 patients had oral treatment only. Intravenous administration made 55% of these patients seizure-free, whereas oral administration produced lasting seizure control in only 9.1%. During chronic oral treatment, it was most difficult to obtain adequate plasma concentrations in 69.1% of the patients, and 43.6% had side effects, most of which were related to very high plasma concentrations. In conclusion, in the first 2 years of life, intravenous administration of PHT is useful for SE, but oral treatment is poorly effective with difficulty to achieve appropriate and stable therapeutic plasma concentrations, and with frequent side effects.

Keywords: Phenytoin; Status epilepticus; Epilepsy; Infant; Newborn

1. Introduction

Phenytoin (PHT) is one of the most commonly used anticonvulsant drugs. The spectrum of activity includes simple and complex partial and generalized tonic-clonic seizures, generalized convulsive and simple or complex partial status epilepticus, and neonatal seizures. PHT is not useful in the treatment of absence epilepsy, West or Lennox–Gastaut syndromes [1]. In the treatment of partial and secondarily generalized seizures, controlled studies in adults have shown no substantial difference in efficacy between carbamazepine (CBZ), phenobarbital (PB), PHT, primidone and valproate (VPA) [2].

PHT administration for status epilepticus requires adequate monitoring and dose adjustment [3]. Efficacy often needs repeated intravenous administration of PHT. Oral administration following intravenous infusion has been shown to be useful in the management of status epilepticus (SE) in children [3].

PHT is also useful in the treatment of seizures and SE occurring in the neonatal period, during which it is administered intravenously after PB has failed [4]. Therapeutic plasma levels of PHT are difficult to maintain after oral dosing in neonates because of erratic and sometimes incomplete absorption [5,6].

There is controversy as to the bioavailability of PHT in newborn babies and infants [7,8]. However, protein binding is impaired [9]. PHT has a narrow therapeutic range (10–20 mg/l), which is even narrower during the neonatal period (6–14 mg/l) [9,10]. It differs from other currently used antiepileptic drugs (AEDs) by its non-linear elimination kinetics demonstrated both in adults and children [11], including the newborn period [5]. This kinetics, as described by the Michaelis–Menten formula, indicates that small increases in dose can produce large plasma concentrations causing clinical toxicity. Because of the non-linear kinetics, plasma concentration of PHT needs to be measured frequently, and several dosage adjustments may be necessary during the first months of treatment.

The present study was designed to evaluate efficacy and safety of PHT in the treatment of situation-related seizures and epilepsies in the first 2 years of life.

2. Patients and methods

We retrospectively analyzed the clinical history of the 82 patients who had been treated, in the first 2 years of life, between 1990 and 1997, with PHT for situation-related seizures or seizures occurring in the course of chronic...
epilepsy, and for whom sufficient data were available regarding clinical history, physical and neurological examinations, drug treatment, laboratory tests (hematology, blood chemistry, AED plasma levels including PHT) and investigations (EEG, brain computed tomography, magnetic resonance imaging).

For each patient, we gathered complete data with particular attention to drug history (age at beginning PHT treatment, route of administration, daily dose, plasma concentration, response to treatment, side effects and comedication).

Syndromes were defined according to the International League Against Epilepsy (ILAE) classification of epilepsy syndromes [12]. Patients were classified in three major syndromic groups: (a) Situation-related seizures in the neonate, (b) Generalized epilepsies, (c) Partial epilepsies. SE was defined clinically and confirmed on EEG recording, as seizures lasting for more than 30 min or as repetitive seizures without return to normal consciousness between seizures [13].

All patients received PHT in the first 2 years of life, either as monotherapy or associated with other AEDs. For some patients it was the first choice drug given intravenously for situation related SE. For others it was given as add-on for intractable seizures after the failure of other AEDs, either orally from onset or orally following intravenous administration for high seizure frequency.

Plasma concentration was considered therapeutic between 10 and 20 mg/l when administered orally for chronic epilepsy, and between 20 and 30 mg/l when administered intravenously (IV).

In this study we considered separately the patients with intravenous treatment and those with oral administration. The schedule for intravenous administration was as previously reported [2] with blood monitoring at predetermined time intervals. Briefly, the initial dose was 15 mg/kg. Administration was repeated every 8 h in order to maintain a phenytoin blood level of between 20 and 30 mg/l.

Following oral administration, three type of responses were considered: ‘total efficacy’ = seizure-freedom for a period of over 3 months; ‘partial efficacy’ = decrease in seizure frequency of over 50% for a period of over 3 months; ‘no efficacy’ = persistence of seizures or decrease in frequency lasting less than 3 months. Following intravenous administration for SE, two types of effects were considered: ‘total efficacy’ = interruption of SE; ‘no efficacy’ = persistence of SE.

3. Results

The study included 82 patients, 42 females and 40 males. Age at seizure onset ranged from birth to 24 months (mean = 3.8 months). Patient classification according to seizure disorders and etiology is shown in Table 1. Age at the beginning of PHT treatment ranged from 1 day to 24 months (mean = 7.4 months).

Patients were included into one of the following groups: group 1 was comprised of 60 patients treated with intravenous PHT for situation-related SE or for SE occurring in the course or at the beginning of chronic epilepsy; group 2 comprises 55 patients who received oral PHT since the very beginning or following initial intravenous administration. Thirty three patients treated with both routes of administration (IV and oral) were included in both groups.

Group 1 includes 60 patients receiving intravenous PHT
for situation-related SE or for SE occurring in the course or at the beginning of chronic epilepsy. It includes 21 patients (35%) with neonatal situation-related seizures, 20 (33.3%) with generalized epilepsy and 19 (31.7%) with partial epilepsy. There was no significant difficulty reaching and maintaining therapeutic blood concentrations with the schedule previously mentioned [3].

Total efficacy was observed in 33 patients (55%), 85.7% of those with neonatal situation-related, but only 30% of those with generalized epilepsy and 47.3% of those with partial epilepsy. Of the responder patients, 18 (54.5%) had neonatal situation-related seizures, six (18.2%) generalized epilepsy, and nine (27.3%) partial epilepsy.

Group 2 included the 55 patients receiving oral PHT either since the very beginning (40%) or following initial intravenous administration (60%). Twenty eight patients (50.9%) had generalized and 27 had (49.1%) partial epilepsy.

In 92.7% of patients PHT was combined with other AEDs. The most frequently associated were vigabatrin, carbamazepine (CBZ), clonazepam, clobazam, phenobarbital (PB) and valproate (VPA).

It was most difficult to determine the proper dose of PHT for 38 patients (69.1%). Clinical side effects were observed in 43.6% of the cases. The most frequently reported were drowsiness, gingival hyperplasia, sleep troubles, hyperactivity, ataxia and movement disorders (Table 2). During chronic treatment, 40% of patients had PHT plasma concentrations over of 20 mg/l.

Only two patients (3.6%) responded totally to treatment and three (5.5%) partially, whereas 50 (90.9%) had no benefit. All five patients with total or partial benefit suffered from partial epilepsy (four symptomatic and one cryptogenic). Thus 18.2% of patients with partial epilepsy responded (total efficacy in 7.4%, partial efficacy in 11.1%) whereas none of those with generalized epilepsy did so.

Characteristics of responders are shown in Table 3: age at onset of epilepsy ranged from 26 days to 7 months (mean = 3.6 months), age of onset of PHT treatment from 6 to 22 months (mean = 12.2). All patients were receiving comedication.

For four of the five responders, treatment was non satisfactory because of time lag to response (two cases), high plasma concentrations (two cases), and/or major side effects (two cases).

Duration of therapeutic effects ranged from 3 to 40 months. It was transient, lasting 3 to 8 months in three patients started on PHT in the first year of life. In two patients started on PHT at 18 and 22 months, duration of efficacy was respectively 40 and 9 months, after which the drug was withdrawn without relapse.

4. Discussion

Based on our results, we believe that, in the first 2 years of life, intravenous administration of PHT is useful for neonatal situation-related seizures or SE, and for SE complicating chronic epilepsy. However, chronic oral treatment should not be advised because of inefficacy, difficulty to achieve therapeutic plasma levels and frequent occurrence of side effects.

In the newborn baby the vast majority of seizures is situation-related. In most cases, seizures are due to organic brain damage of perinatal origin or to acute metabolic disturbances. Most neonatal seizures are short-lived events, even when brain damage has been produced, and they do not herald a chronic convulsive disorder. Nevertheless, they are rarely single, but are often repeated over a period of a few days and may result in SE [14], requiring immediate and vigorous treatment. The goal of treatment is to stop convulsions, in order to prevent worsening of brain damage due to autonomic disorders or eventually to seizure activity.

AEDs mostly utilized to control neonatal seizures are traditionally PB, PHT and benzodiazepines (BZ). At this age, BZ are not the first choice drugs, because of their major side effects including respiratory and cardiovascular depression, sedation, hypotonia and salivation. PB is most often used as the first line drug. PHT is administered intravenously after PB has failed [3]. PHT is an effective drug if dose adjustments are made on the basis of plasma concentrations.

In infancy, chronic epilepsy is often characterized by frequently recurring seizures that may end in SE needing prompt treatment to limit worsening of the neurological condition [15]. Thus, PHT could also be useful in the management of SE in this context. Indeed, intravenous administration of PHT for SE proved to be most useful in the present series, both in neonatal situation-related seizures and in acute worsening of chronic epilepsy.

When the drug is administered IV with good results, it may be tempting to pursue the treatment via oral administration to prevent recurrence of seizures. Richard et al. (1993) [3] showed that intravenous administration of PHT for cluster seizures or SE produces a high rate of seizure

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Table 2

<table>
<thead>
<tr>
<th>Effect</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>12</td>
</tr>
<tr>
<td>Gingival hyperplasia</td>
<td>8</td>
</tr>
<tr>
<td>Sleep troubles</td>
<td>8</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>6</td>
</tr>
<tr>
<td>Ataxia</td>
<td>5</td>
</tr>
<tr>
<td>Movement disorders</td>
<td>4</td>
</tr>
<tr>
<td>Loss of weight</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2</td>
</tr>
<tr>
<td>Cognitive disturbances</td>
<td>2</td>
</tr>
<tr>
<td>Behavior disturbances</td>
<td>1</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1</td>
</tr>
</tbody>
</table>

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Table 3
Clinical characteristics of responders

<table>
<thead>
<tr>
<th>Type of epilepsy</th>
<th>Etiology</th>
<th>Onset epilepsy</th>
<th>Onset PHT (mo.)</th>
<th>Route of administration</th>
<th>Efficacy of treatment</th>
<th>Complexity of treatment</th>
<th>Time lag to efficacy</th>
<th>PHT dosage (mg/kg)</th>
<th>Plasma concentration PHT (mg/l)</th>
<th>Comedication</th>
<th>Side effects</th>
<th>Efficacy duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CPE</td>
<td>Unknown</td>
<td>6 months</td>
<td>6</td>
<td>IV &gt; Oral</td>
<td>Total</td>
<td>Partial</td>
<td>0</td>
<td>13</td>
<td>10</td>
<td>VGB</td>
<td>CBZ-STP, Gingival hyperplasia, loss of weight, Drowsiness</td>
<td>3 months</td>
</tr>
<tr>
<td>2 SPE</td>
<td>Pelizaeus syndrome</td>
<td>2.5 months</td>
<td>6</td>
<td>Oral</td>
<td>Partial</td>
<td>0</td>
<td>0</td>
<td>25-50</td>
<td>7.5-40</td>
<td>VGB</td>
<td>CBZ-STP, Cognitive disturbance</td>
<td>8 months</td>
</tr>
<tr>
<td>3 SPE</td>
<td>Multiple cerebral malformations</td>
<td>1.5 months</td>
<td>9</td>
<td>Oral</td>
<td>Partial</td>
<td>15 days</td>
<td>20</td>
<td>19-25.7</td>
<td>VGB</td>
<td></td>
<td></td>
<td>8 months; died at 17 months</td>
</tr>
<tr>
<td>4 SPE</td>
<td>Multiple cerebral malformations</td>
<td>7 months</td>
<td>18</td>
<td>IV &gt; Oral</td>
<td>Total</td>
<td>0</td>
<td>9</td>
<td>6</td>
<td>CBZ-PG, Cognitive disturbance</td>
<td></td>
<td></td>
<td>40 months*</td>
</tr>
<tr>
<td>5 SPE</td>
<td>Tuberous sclerosis</td>
<td>26 days</td>
<td>22</td>
<td>Oral</td>
<td>Partial</td>
<td>28 days</td>
<td>8</td>
<td>6</td>
<td>CBZ-VGB</td>
<td></td>
<td></td>
<td>9 months*</td>
</tr>
</tbody>
</table>

*a CPE, cryptogenic partial epilepsy; SPE, symptomatic partial epilepsy; IV, intravenous; VGB, vigabatrin; *drug withdrawn without relapse; CBZ, carbamazepine; STP, stiripentol; PG, progabide.
Sometimes, epileptic seizures may be exacerbated by cerebellovestibular signs and symptoms. With increasing and elevated health costs, effects. This proved to produce considerable loss of time to response, high plasma concentrations, and side difficulties in the management of treatment because of long lag time. Moreover, four of the five responders exhibited major difficulties, requiring many plasma level determinations and a long time spent in hospital for adequate monitoring. In addition, there is no reason why the effect of PHT on the brain should be poor with oral administration but high via intravenous route. The main reason for poor efficacy seems to be related to plasma concentrations required to control seizures at this age. Half life is very short in infancy and bioavailability controversial, plasma concentrations are therefore likely to vary considerably over the day, and this could prevent reaching adequate and stable brain concentrations, between ineffective and toxic values. It has been shown that hectic benzodiazepine blood levels following repeat intrarectal administration in patients with intractable epilepsy are much less likely to generate seizure control than stable levels produced by regular oral administration.

In the present series, it was most difficult to maintain adequate plasma concentrations with oral administration of PHT, and for most patients we failed, although monitoring was intensive. The high frequency of overdosage could be related to the greater difficulty in the management of PHT at this age. Moreover, major side effects affected 43.6% of these patients, most of which were related to very high plasma concentrations. Treatment was remarkably complex, requiring many plasma level determinations and a long time spent in hospital for adequate monitoring. Moreover, four of the five responders exhibited major difficulties in the management of treatment because of long lag time to response, high plasma concentrations, and side effects. This proved to produce considerable loss of time and elevated health costs.

As reported in several reviews, side effects are most frequent during PHT treatment and are characterized by cerebellovestibular signs and symptoms. With increasing dose, cognitive and sedative effects are observed. Sometimes, epileptic seizures may be exacerbated.

In acute situations in newborn and infants requiring intravenous AED administration, the conditions of the patient is such that side effects are easily overlooked and higher plasma concentrations thus seem to be better tolerated. In addition, the IV route combined with intensive pharmacokinetic monitoring is likely to produce less variations in blood levels. On the other hand, the occasional cause of the seizure cluster usually clears spontaneously over a few days, thus requiring no chronic treatment. There is general agreement that no chronic treatment is required following neonatal convulsions, provided the EEG demonstrates no paroxysmal activity when the patient is delivered from hospital.

References

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