Valproate reduces spontaneous generalized spikes and waves but not photoparoxysmal reactions in patients with idiopathic generalized epilepsies


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**SUMMARY**

**Purpose:** Patients with idiopathic generalized epilepsies (IGEs) often present with interictal spike-wave discharges (SWDs) at rest (spontaneous SWDs), during hyperventilation, and in response to photic stimulation (photoparoxysmal response or PPR). Valproic acid (VPA) is a first-line antiepileptic drug for therapy of patients with IGE. Herein we investigated the effect of VPA on all three types of SWDs in children and adolescents with IGE.

**Methods:** Routine electroencephalography (EEG) during wakefulness, which was recorded before VPA monotherapy and up to four times during the first year of the VPA treatment, was analyzed retrospectively. For the analysis of the VPA effect on spontaneous SWDs and SWDs under hyperventilation, the number and duration of SWDs were counted. SWDs under intermittent photo stimulation (IPS) were classified according to the extent of propagation (grading). Response to VPA treatment (rest/hyperventilation) was defined as a disappearance of SWDs within the year after VPA introduction.

**Key Findings:** Eighty-four patients (37 male and 47 female, mean age 9.5 ± 4.1 years) exhibited spontaneous SWDs or SWDs under hyperventilation. From this sample, 34 patients exhibited the PPR (7 male and 27 female, mean age 10.1 ± 3.9 years). A significant reduction in the number and duration of spontaneous SWDs and SWDs under hyperventilation was observed in the first 6 weeks of treatment (p ≤ 0.001, corrected, 87.3% responders). This effect remained stable over the 1 year observation period. Concerning PPR, only 4 (12.9%) of 31 patients were classified as responders. The difference between groups of patients with spontaneous/induced SWDs and PPR according to the number of responders was significant (p < 0.001).

**Significance:** This study provides evidence that the effect of VPA on SWDs differs dependent on the types of SWDs. In the majority of patients, spontaneous SWDs and SWDs under hyperventilation disappeared, whereas the PPR mostly remained under VPA treatment. These results point to different pathogenetic mechanisms underlying the spontaneous and the evoked generalized epileptic activity in the EEG.

**KEY WORDS:** Photoparoxysmal reaction, Idiopathic generalized epilepsy, Valproate therapy, Valproate effect.

Photoparoxysmal response (PPR) is a highly heritable electroencephalographic trait consisting of spike-and-wave paroxysms in response to visual stimulation (Fisher et al., 2005). PPR is a frequent feature of idiopathic generalized epilepsies (IGEs) and represents a genetic risk factor predisposing to IGE (Stephani et al., 2004). It has been suggested that spontaneous and evoked interictal epileptiform discharges are related to distinct neurophysiologic mechanisms. Spontaneous 3 Hertz spike-wave paroxysms as well as polyspike-and-wave paroxysms are associated with activation of typical central nervous system (CNS) networks involving the thalamus, medial frontal cortex, parietal cortex, and precuneus (Moeller et al., 2008). Evoked paroxysms such as PPR are related to activation of a cortical network consisting of visual and parietal as well as prefrontal cortex (Moeller et al., 2009). It can be hypothesized that the different pathophysiologic pathways of spikes and waves also result in different responses to antiepileptic medication.

Valproate (VPA) is the drug of first choice for treatment of IGE (Curatolo et al., 2009). During VPA treatment, the spontaneous spike-wave discharges (SWDs) disappear in the majority of patients (Bruni et al., 1980; Stefan et al., 1981). Concerning PPR, the results of VPA treatment studies are equivocal. Whereas a number of studies have demonstrated a clear reduction of PPR under VPA (Harding et al., 1997; Verrotti et al., 2004), some authors showed an effect...
of VPA on voltage, morphology, duration, and pattern of propagation of visually induced SWDs, but to a lesser degree on the frequency of occurrence. These studies suggest that VPA reduces the spread of epileptic activity from the trigger site, but it may have relatively little influence on the trigger mechanism (Darby et al., 1986). We, therefore, investigated the effect of VPA monotherapy on spontaneous SWDs, SWDs during hyperventilation, and intermittent photic stimulation (IPS) in patients with IGE.

**METHODS**

From 1975 to 2005, all patients classified as having IGE in the Department of Neuropediatrics, University Children’s Hospital, Kiel were analyzed retrospectively. Routine electroencephalography (EEG) during wakefulness (20 min in each subject), which was recorded before the first-line VPA monotherapy and up to four times during the first year of the VPA monotherapy of children with IGE, was selected for further analysis. Five observation periods were determined: period 0 (before treatment), period 1 (30 ± 16 days after treatment onset), period 2 (90 ± 30 days after treatment onset), period 3 (180 ± 60 days after treatment onset), and period 4 (360 ± 90 days after treatment onset). Diagnosis of IGE was made according to the International League Against Epilepsy (ILAE) (Commission, 1989) classification scheme.

SWDs were identified in recordings performed at rest (spontaneous SWDs), during hyperventilation and during IPS. For the analysis of the effect of VPA on spontaneous SWDs and SWDs under hyperventilation, the number and duration of SWDs were counted. Because of ethical concerns, every IPS was stopped after the first affirmation of the PPR. Therefore, the counting of PPR was not possible. SWDs under IPS were classified according to the extent of propagation (see below). The effect of VPA on SWDs at rest, during hyperventilation, and during IPS was defined using responder criterion: response to VPA treatment means the disappearance of SWDs during the four observation periods after VPA introduction. Seizure control of VPA treatment was defined as achievement of seizure freedom during the first year of treatment.

**Electroencephalographic assessment of the PPR**

IPS was carried out with a standard photostimulator (Knott [Munich, Germany] or Grass PS22 [Quincy, MA, USA] stimulator) in a dim room. The lamp distance was approximately 25 cm. For 30 s, the flash frequency was slowly increased up to 20/s, and for the next 30 s reduced to 4/s. Thereafter, flash frequencies of 5, 10, 12, 15, 20, and 25/s were used for 20 s each and irregular frequencies for a period of 30 s. During each 30 s period the effect of three eye conditions (eye closure, eyes closed, and eyes open) was tested once. Two experienced EEG specialists analyzed EEG studies independently and classified each as PPR with occipital spikes or PPR with propagation according to Harding and Fylan (1999). PPR with occipital spikes was always confined to posterior regions of the scalp and corresponds to PPR type I and II according to the classification proposed by Waltz et al. (1992). The PPR was labeled as PPR with propagation when (1) the appearance of parietooccipital spikes was followed by biphasic slow waves spreading to frontal cortex or (2) when the PPR consisted of generalized spike-and-wave discharges (PPR type III and IV according to Waltz et al., 1992).

**Statistics**

Statistical analysis was performed using the SPSS 13.0 program (SPSS Inc. Chicago, IL, U.S.A.). For the analysis of the VPA effect on spontaneous SWDs and SWDs under hyperventilation, differences in mean values (standard deviation, SD) of the number and duration of SWDs between observation periods (baseline vs. periods 1–4) were analyzed using the two-tailed paired-sample *t*-test. For the analysis of the VPA effect on PPR only, descriptive statistics were used. Differences in the responder status of PPR and spontaneous/induced SWDs during VPA therapy were analyzed using the Fisher’s exact test. A two-sided *p*-value of <0.05 was considered statistically significant. Bonferroni alpha adjustment was applied for correction for multiple comparisons (16 tests).

**RESULTS**

**Sample of the study**

Of 201 patients with IGE found in the database of the Department of Neuropediatrics, 111 patients received valproate (VPA) monotherapy. Eighty-four patients (37 male and 47 female, mean age 9.5 ± 4.1 years, age range from 2.1 to 17.5 years) exhibited spontaneous SWDs at rest or SWDs under hyperventilation. From this sample, 67 patients underwent IPS for study of the PPR. Thirty-four patients exhibited the PPR. For particular diagnosis and demographic data see Table 1.

Four patients were not investigated with IPS before treatment and were excluded from further analysis. Twenty-four of the remaining 30 patients (80%) with PPR were characterized by generalized PPR (grade 4). These 30 patients were followed. Seventeen patients exhibited PPR only at regular frequencies, 12 patients at regular and random frequencies, and one patient expressed PPR only at random frequencies. During the first observation period, the mean VPA dosage was 21.2 mg/kg, which remained stable during the second (22.1 mg/kg), third (21.6 mg/kg), and fourth periods (19.6 mg/kg). The mean serum values were 73.1, 71.4, 70.8, and 72.7 mg/L, respectively.

**Effect of VPA**

After the commencement of VPA therapy, a significant reduction in the number and duration of spontaneous SWDs...
was observed in the first 6 weeks of treatment (Fig. 1). This effect remained stable over the 1-year observation period. No significant differences between periods 2, 3, and 4 were found. VPA furthermore exerted a significant effect on the SWDs under hyperventilation. The most pronounced reduction in both the number and duration of SWDs/20 min under hyperventilation was detected also in the first 6 weeks of the treatment (from period 0 to period 1).

PPR was eliminated in four and reduced to a lower grade in an additional four children (Fig. 2). Seventeen patients with the propagated PPR and five patients with the localized PPR exhibited no changes in the PPR. Four patients showed a decreased grade of PPR (propagated to local) during VPA therapy. One patient developed PPR during therapy for the first time. Concerning spontaneous SWDs and SWDs under hyperventilation, 87% of patients (55 of 63) were classified as responders: they no longer exhibited PPR under VPA treatment. These four patients were diagnosed with juvenile myoclonic epilepsy (JME), childhood absence epilepsy (CAE), and two patients with generalized tonic clonic seizures (GTCS) alone. All PPR responders became seizure free in the first year of VPA treatment. In 26 of 27 non-PPR responders, seizures were controlled by VPA successfully. One patient with GTCS seizures relapsed because of noncompliance. The better compliance led to a complete control of seizures by VPA even in this patient. The difference between groups of patients with spontaneous/induced SWDs and PPR according to the number of responders was significant (p < 0.001, Table 2).

**Discussion**

This study provides evidence that the effect of VPA on SWDs differs dependent on the types of SWDs. In the majority of patients (>80%) with IGE, spontaneous SWDs and SWDs induced by hyperventilation disappeared, whereas the PPR mostly remained under VPA treatment. The effect (abolition) of VPA on spontaneous SWDs and SWDs induced by hyperventilation was associated with the seizure freedom under VPA in 87% of patients (55 of 63). Only in two patients spike and wave activity persisted, whereas seizures disappeared. In six patients with absence epilepsy both spike and wave activity and seizure activity persisted. It seems likely that the effect of VPA on spontaneous SWDs is a good predictor for clinical efficacy of this drug. In contrast, there was no association between the effect of VPA on PPR and on seizure frequency. Even in all four patients with photogenic seizures, PPR persisted but seizures were controlled by VPA therapy.

The distinct reaction of different spikes to VPA treatment was also observed by Anyanwu et al. (2004), who investigated 33 patients with photosensitive epilepsy and demonstrated that spontaneous SWDs disappeared during VPA treatment, whereas the occipital spikes persisted. The authors suggested that this effect could be due to a time-dependent functional disability of certain cells of the visual system to respond positively to the VPA’s modulatory activity. Harding et al. (1978, 1997) and Verrotti et al. (2004) demonstrated a stronger effect of VPA on PPR than in our study (in 4 of 30 patients): PPR disappeared in 27 of 50 patients, in 23 of 56 treated patients, and in 15 of 40 patients, accordingly. In these studies, however, about half of the VPA-treated children showed ongoing evidence of photosensitivity in the EEG. Mentionable is the outcome of VPA treatment in the study by Harding et al. (1997) that demonstrated persistence of PPR in at least two thirds of patients with photosensitive epilepsy. Even in a great proportion of patients the PPR was degraded from the generalized PPR to nonresponder expression a reduced number of spike-and-wave discharges, but seizures were controlled by VPA successfully. Concerning PPR, only four of 31 patients were classified as responders: they no longer exhibited PPR under VPA treatment. From these eight patients, absence seizures were not controlled by VPA in six. The medication was changed to lamotrigine (n = 2) or ethosuximide (n = 4). Two of eight

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**Table 1. Classification and demographic data of 84 patients with idiopathic generalized epilepsy who exhibited spontaneous SWDs and SWDs induced by hyperventilation**

<table>
<thead>
<tr>
<th>IGE patients with spontaneous SWDs</th>
<th>84</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAE</td>
<td>33</td>
</tr>
<tr>
<td>JAE</td>
<td>25</td>
</tr>
<tr>
<td>Epilepsy with generalized tonic-clonic seizures alone (GTCS)</td>
<td>14</td>
</tr>
<tr>
<td>JME</td>
<td>8</td>
</tr>
<tr>
<td>Epilepsy with photosensitive seizures</td>
<td>4</td>
</tr>
<tr>
<td>Male</td>
<td>37</td>
</tr>
<tr>
<td>Female</td>
<td>47</td>
</tr>
<tr>
<td>Mean age (years) ± SD</td>
<td>9.5 ± 4.1</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>2.1–17.5</td>
</tr>
<tr>
<td>Patients who underwent IPS</td>
<td>67</td>
</tr>
<tr>
<td>Patients who exhibited PPR</td>
<td>34</td>
</tr>
<tr>
<td>CAE</td>
<td>10</td>
</tr>
<tr>
<td>JAE</td>
<td>8</td>
</tr>
<tr>
<td>Epilepsy with generalized tonic-clonic seizures alone (GTCS)</td>
<td>7</td>
</tr>
<tr>
<td>JME</td>
<td>5</td>
</tr>
<tr>
<td>Epilepsy with photosensitive seizures</td>
<td>4</td>
</tr>
<tr>
<td>Males</td>
<td>7</td>
</tr>
<tr>
<td>Females</td>
<td>27</td>
</tr>
<tr>
<td>Mean age (years) ± SD</td>
<td>10.1 ± 3.9</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>2.9–16.9</td>
</tr>
</tbody>
</table>

Sixty-seven of these patients underwent photostimulation (IPS) during VPA therapy.

JAE, juvenile absence epilepsy.
the occipital spikes only. The higher response of PPR on VPA may be explained by a difference in stimulation protocols. The studies by Harding et al. (1978, 1997) and Verrotti et al. (2004) used more separate and higher frequencies during stimulation; they did not apply stimulation with the random mode of frequencies (see Harding et al., 1997). Although the differences between protocols have not been proven systematically through a direct comparison, the following arguments led us to suggest the equal efficacy of both protocols: (1) the protocol of this study implements the most frequencies that have been demonstrated as most epileptogenic (Harding & Harding, 1999) and (2) according to our clinical experience, the irregular stimulation with the random mode of frequencies may elicit photosensitivity even in patients who did not produce PPR under standard stimulation according to Harding et al. (1997), but this is not common. Most of the patients who express PPR with the irregular stimulation are showing PPR also with regular frequencies. In our study only one patient expressed PPR with the irregular stimulation and not with regular frequencies. This patient would probably not have been detected in the protocol by Harding et al. (1978, 1997). Moreover, the long-term follow-up in the study of Verrotti et al. (2004) (mean duration 8 years) and Harding et al. (1997) (mean duration 14 years) may additionally account for differences between studies, whereas our study period lasted 3 years only. Harding et al. (1997) described an abolishment of PPR even in 14 of 46 patients in the untreated group of patients. Age dependence of PPR may also explain the high rate of abolishment of PPR. During this long observation period, developmental changes in sensitivity of the visual system toward synchronizing effects of IPS may occur (Kasteleijn-Nolst Trenite, 1994). Particularly, developmental changes in the balance between the glutamatergic and γ-aminobutyric acid (GABA)ergic neurotransmission may be responsible for changes of VPA effect over time (Pinto et al., 2010). Finally, the findings of our study are consistent with the observations of Darby et al. (1986), who demonstrated an effect of VPA on voltage, morphology, duration, and pattern of propagation of visually induced SWDs, but to a lesser degree on the prevalence of PPR. These authors suggested that VPA reduces the spread of epileptic activity from the trigger site, but it may have relatively little influence on the trigger mechanism (Darby et al., 1986). Indeed, our studies on transcranial magnetic stimulation and visual evoked potentials in PPR revealed different changes of cortical excitability in the visual cortex in patients with occipital spikes only and patients with propagated PPR (Siniatchkin et al., 2007a) (Siniatchkin et al., 2007b). Because PPR with propagation is characterized by an increased glutamatergic neurotransmission (Shepherd & Siniatchkin, 2009), and VPA exerts its antiepileptic effect

Figure 1.
Changes of duration and number of spontaneous generalized SWDs (A, B) and SWDs during hyperventilation (C, D) under VPA therapy. Reduction is shown in the first 6 weeks of treatment (observation periods 1 and 2). The effect remained stable over observation periods 2–4 in the first year of treatment. T-values are shown for comparison between the observation period 0 (baseline before treatment) and all other observation periods after treatment onset (for spontaneous SWDs: d.f. = 63; all p ≤ 0.001, for SWDs during hyperventilation: d.f. = 59; all p < 0.001, all p-values survived Bonferroni alpha adjustment. No statistical differences were found between periods 1 and 2, 2 and 3, or 3 and 4 for both spontaneous SWDs and SWDs under hyperventilation). Epilepsia © ILAE
on the basis of its antiglutamatergic properties (reducing field excitatory postsynaptic potential slope and excitability ratio) (Kim et al., 2007), the influence of VPA on the propagation but not on the trigger mechanisms of the PPR appears plausible.

The current study supports our previous observations that spontaneous SWDs and PPR are associated with different pathophysiologic mechanisms. Simultaneous recordings of EEG and functional magnetic resonance imaging (fMRI) have shown that the spontaneous SWDs were related to positive blood oxygenation-level dependent (BOLD) signal changes in the thalamus and negative BOLD responses in the brain areas of the default mode network and the caudate nucleus (Moeller et al., 2008). In contrast, the PPR is a cortical phenomenon only according to these studies; EEG-fMRI has revealed positive BOLD signal changes in the occipital, parietal, and prefrontal cortices associated with PPR, but no hemodynamic changes in the subcortical gray matter (Moeller et al., 2009). VPA seems to exert different effects on the described networks. It has been suggested repeatedly that the main antiepileptic effect of VPA on SWDs is delivered by changes in the thalamocortical mechanisms (Crunelli & Leresche, 2002). Although VPA may decrease cortical excitability (Ziemann, 2004), whether the cortical effects of VPA alone are sufficient or additional thalamocortical mechanisms are necessary to reduce susceptibility of the brain for SWDs must be investigated in further studies.

**Conclusion**

VPA treatment significantly reduces SWDs at rest, but reduces SWDs induced by IPS to a much lesser extent. These results point to possibly different pathogenetic mechanisms underlying the spontaneous and the induced generalized epileptic activity in the EEG.

**ACKNOWLEDGMENT**

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**Disclosure**

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

**References**


