What is the relative value of the standard anticonvulsants: Phenytoin and fosphenytoin, phenobarbital, valproate, and levetiracetam?

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Status epilepticus (SE) is a serious epileptic condition associated with significant morbidity and mortality that requires prompt medical management. Outcome is largely contingent on the age of the patient, the etiology, and the duration of the condition before treatment with antiepileptic drugs (AEDs) (Towne et al., 1994; Delorenzo et al., 1999). Treatment is evolving as new medications become available. This summary will give a brief overview on the use of phenytoin (PHE), fosphenytoin (fPHE), valproic acid (VPA), phenobarbital (PB), and levetiracetam (LEV) in generalized convulsive status epilepticus (GCSE).

**Currently Used First-Line AEDs: Benzodiazepines**

First-line treatment for GCSE is intravenous administration of 4 mg of lorazepam (LZP) or 10 mg of diazepam (DZP) directly followed by 15–18 mg/kg of PHE or equivalent fPHE (Meierkord et al., 2006) (Alldredge et al., 2001) (Treiman et al., 1998; Prasad et al., 2005, 2007). The advantage of LZP over DZP or midazolam is its long-lasting clinical effect, which is determined by the pharmacologic properties of the drug. DZP is more lipophilic and is subject to extensive redistribution, thereby decreasing the concentration of DZP in the brain (Trinka, 2009). However, clonazepam has pharmacokinetics properties similar to that of LZP and is also widely used in some European countries, but comparative studies are not available. There is wide agreement that any recommendation of first-line treatment in SE includes LZP, depending on its availability in the given country (Shorvon et al., 2008). Results from two large randomized controlled trials (RCTs) investigating the efficacy of treatments in the first stage of SE reveal that the most effective drug, LZP, was successful in 65% and 59% of the treated patients (Treiman et al., 1998) (Alldredge et al., 2001). Therefore, at least one-third of patients with SE will need a second-stage treatment, but there are virtually no adequate studies available that compare different treatment regimens in established status after benzodiazepines (BZPs) have failed.

**Phenytoin and Fosphenytoin**

The main advantage of PHE is the lack of a sedating effect. However, a number of potentially serious adverse effects may occur. Arrhythmias and hypotension have been reported, particularly in patients older than 40 years (Cranford et al., 1978, 1979). In addition, local irritation, phlebitis, and dizziness may accompany intravenous administration of PHE. Although intravenous PHE has been available since 1956 (Carter, 1958), it was not until 1968 that adequate doses were used to successfully treat SE (Wallis et al., 1968). Experience is used as an argument in favor of PHE; however, there are only six studies available as full reports including 595 patients (adults and children) with various forms of SE (McWilliam, 1958; Leppik et al., 1983) (Waller et al., 1977) (von Albeert, 1983) (Treiman et al., 1998). The overall success rate with intravenous PHE has ranged from 44% in the randomized controlled study to 90% in the uncontrolled studies. It is important to consider that many of the patients in these studies had ineffective pre-treatment with BZPs, paraldehyde, or PB, making an estimate of the effect of PHE difficult to assess. In the VA study (Treiman et al., 1998) and in another randomized study from India (Misra et al., 2006), PHE was used as a first-line treatment in the early phase of SE with success rates of 44% and 42%, respectively.

The water-soluble prodrug of PHE, fosphenytoin (fPHE), has been approved for treatment of SE since 1996 (U.S. Food and Drug Administration, FDA). Although it partially overcomes some of the major problems associated with use of PHE (e.g., local irritation), it is expensive,
and many hospital formulary committees are unwilling to pay the difference.

**Phenobarbital**

Phenobarbital (PB) is one of the oldest AEDs still in clinical use, but its value in the treatment of SE is controversially discussed. PB has fallen out of favor in many countries across Europe because of anecdotal evidence of hypotension, arrhythmias, and hypopnea. In fact there are only limited studies available assessing the efficacy of PB in SE. Shaner et al. (1988) compared prospectively the efficacy of 18 patients treated with PB and 18 patients treated with PHE+DZP. PB was given at a dose of 100 mg/min until 10 mg/kg had been reached. Sixteen of 18 patients (89%) were rapidly controlled with PB, although two of them received additional PHE. The mean time to control seizures with PB was 5 min compared to 9 min with PHE+DZP. Two of 18 patients (11%) with PB had hypotension and one of 18 had arrhythmias. PB was also used as one of four treatments in the VA study (Treiman et al., 1998). In this study, 15 mg/kg of PB at 100 mg/min controls 58% of patients with a verified diagnosis and 24% of patients with subtle status. There was no difference in efficacy compared to the LZP group. Although adverse events with PB were frequent, with 34% hypotension, 13% hypoventilation, and 3% arrhythmias, there was no difference compared to the other treatment groups. In the VA study, serum levels of 31.2 ± 37.2 µg/ml were achieved after infusion. Serum levels of ≥70 µg/ml will compromise the level of consciousness in all patients and might, therefore, contribute to postictal coma. The polypropylene solvent may cause local irritation, necrosis, or hemolysis and infusion syndrome after prolonged use. Its use in established SE is widely accepted (Shorvon et al., 2008).

**Valproate**

The availability of intravenous VPA since the 1980s provides an interesting alternative, since PHE/iPHE cannot be used in all patients, including those with allergic reaction to PHE and some forms of progressive myoclonus epilepsy. In addition, elderly patients and cardiorespiratory unstable patients may be at increased risk for adverse reactions associated with PHE/iPHE (Cranford et al., 1978). A number of studies on intravenous VPA used to control various types of SE (GCSE, partial NCSE, status myoclonus, and absence status) in a variety of patient populations, ranging from children to elderly patients with cardiovascular instability, showed a low incidence of adverse events, in particular, no hemodynamic adverse effects (Sinha & Nariotoku, 2000), even when VPA was administered at higher than recommended infusion rates (Wheless et al., 2004) (Venkataraman & Wheless, 1999) (Limdi & Faught, 2000; Limdi et al., 2005, 2007). To date there are 19 prospective or retrospective series and three randomized open trials published including 633 adults or children [recently reviewed in (Trinka, 2007b)]. These studies suggest that intravenous VPA is as effective as PHE/iPHE in resolving SE in patients who have previously failed conventional first-line therapies such as BZPs. Success rate between 60% and 83% have been reported. In approximately 75% of cases, seizure control was achieved during VPA infusion or within 20 min. Three recent randomized comparative trials from India deserve some further comments. One study compared intravenous VPA with intravenous PHE as first-line treatment (Misra et al., 2006). The results favor intravenous VPA (66% vs. 42%), but the study has low statistical power [calculated 95% confidence intervals (CIs) were (50–81%) vs. (26–59%); number needed to treat 4.3 (2.2–429.9) and an inappropriate use of one-sided t-test (Rossetti, 2007). Another study investigated 40 children with refractory SE (aged 5–12 years) (Mehta et al., 2007). Initial treatment for all children was intravenous DZP (0.2 mg/kg) followed by intravenous PHE (20 mg/kg followed by an additional 5–10 mg/kg if seizures did not stop), if necessary. Nonresponders were randomized to intravenous VPA (30 mg/kg over 2–5 min, followed as needed by a 10 mg/kg bolus 10 min later, and then by infusion at 5 mg/kg per hour) or DZP infusion (at 10 µg/kg/min, increased every 5 min if seizures continued, until control or 100 µg/kg/minute was reached). Treatment failures received thiopental. The reported success rates were 80% for VPA and 85% for DZP. There was a statistically significant (p < 0.01) advantage for VPA regarding the central depressant effects. Although none of the children in the VPA group had arterial hypotension or hypopnea leading to ventilatory support, 60% of those in the DZP group required ventilation. Fifty percent had hypotension and 40% required vasopressors. Ninety-five percent of patients treated with intravenous DZP were admitted to the intensive care unit (ICU), whereas only 55% of the VPA-treated children needed intensive care. Although there was no difference in the efficacy, there was a clear advantage of VPA compared to DZP in safety measures. Another study compared intravenous VPA with intravenous PHE treatment after BDZs have failed (Agarwal et al., 2007). Fifty patients were randomized, and according to the publication matched. The success rate was 88% with VPA and 84% with PHE. There was no difference in efficacy or adverse effects between the treatment groups.

The most commonly reported effective doses were between 15 and 45 mg/kg in bolus (6 mg/kg/min) followed by 1 mg/kg per hour infusion. The incidence of adverse events (mainly hypotension, dizziness, and thrombocytopenia) was low (<10%) and independent of infusion rate. Only a few cases of acute VPA encephalopathy were
reported (Embacher et al., 2006), and the pharmacovigilance data reveal no increased incidence of encephalopathy with intravenous use (sanofi aventis data on file; personal communication). This issue has to be carefully addressed in future studies.

Although adequate RCTs are missing, consensus guidelines produced in Belgium (van Rijckevoorsel et al., 2005), Spain (Serrano-Castro et al., 2005), and Germany (Kramer et al., 2005; Kurthen et al., 2008) recommend the use of intravenous VPA as an alternative second-line treatment to PHE in patients with SE who fail to respond to intravenous BZPs. A recent European consensus statement listed intravenous VPA as an option in stage 2 of convulsive SE, when BZPs have failed (Shorvon et al., 2008).

**LEVETIRACETAM**

In 2006, an intravenous formulation of LEV was approved in the European Union for the treatment of patients with epileptic seizures who are temporary unable to swallow. Moreover, it allows the clinician a rapid titration in seizure emergency situations, such as seizure clusters or SE. Intravenous LEV is not licensed for treatment of SE, but has been widely used since it was available and several open case series are published (Faroq et al., 2007; Knake et al., 2007; Schulze-Bonhage et al., 2007; Abend et al., 2008; Altenmüller et al., 2008; Goraya et al., 2008; Ruegg et al., 2008) [recently reviewed in (Trinka & Dobesberger, 2009)]. LEV has a wide spectrum of action and a favorable pharmacokinetics profile. The mechanism of action is unknown but seems to involve the synaptic vesicle protein 2A (SV2A). The pharmacodynamic mechanisms appear distinct from that of classic AEDs and unrelated to known mechanisms of neurotransmission (Surges et al., 2008). In addition, neuroprotective effects have been described in animal models (Gibbs et al., 2006). The intravenous formulation is bioequivalent to the oral preparation and it is well tolerated even at higher doses and/or at faster infusion rates than reported (Ramael et al., 2006a,b).

Open label experience with retrospective case series is accumulating, and until now 156 patients who were treated with intravenous LEV for various forms of SE have been reported, with an overall success rate of 65.4% (Trinka & Dobesberger, 2009). The most often used initial dose was 2,000–3,000 mg/day over 15 min. Adverse events were reported in 7.1%, and these were mild and transient.

Although intravenous LEV is an interesting alternative for the treatment of SE due to the lack of centrally depressant effects and low potential of drug interactions, one has to be aware of the nonrandomized retrospective study design, the heterogeneous patient population and treatment protocols, as well as the publication bias inherent in these types of studies. Only a large RCT with an adequate comparator will reveal the efficacy and effectiveness of this promising new intravenous formulation. However, in a recent consensus document of the International League Against Epilepsy (ILAE) Task Force on Status Epilepticus summarizing the results of the workshop held at the First London Colloquium on Status Epilepticus, intravenous LEV is listed as a “treatment option for the stage of established SE” (Shorvon et al., 2008).

**TREATMENT ALGORITHMS IN EARLY AND ESTABLISHED SE**

As it is evident from the few RCTs in the early stage of SE, LZP is the most effective drug tested in these trials, and, therefore, all available evidence-based recommendations takes this into consideration (van Rijckevoorsel et al., 2005; Serrano-Castro et al., 2005; Meierkord et al., 2006; Minicucci et al., 2006; Kurthen et al., 2008; Shorvon et al., 2008). However, LZP was only successful in 65% and 59% of the treated patients (Treiman et al., 1998) (Aldredge et al., 2001) and other options as first-line treatment, such as clonazepam, were not tested. After failure of LZP, only a further 7.3% of patients will respond to PHE. Effect size for VPA, PB, or LEV after LZP failure is unknown. Evidence-based recommendations for the treatment of established status after failure of LZP are not available, and it has been proposed that treatment options should guide the treating physician until data from a RCT will address the question of best treatment in this stage of SE (Trinka, 2007a; Kurthen et al., 2008; Shorvon et al., 2008).

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