

INTRAVENOUS VALPROATE FOR STATUS EPILEPTICUS . . . AN EFFECTIVE, YET STILL MERELY EMPIRICAL ALTERNATIVE!

Valproate Is an Effective, Well-Tolerated Drug for Treatment of Status Epilepticus/Serial Attacks in Adults. Olsen KB, Taubøll E, Gjerstad L. *Acta Neurol Scand Suppl* 2007;187:51–54. **OBJECTIVE:** Status epilepticus (SE) and serial attacks (SA) represent neurological emergencies, and mortality rate for SE/SA is high, ranging from 3% to 25%, depending on cause and co-morbidity. As SE/SA become more refractory to treatment over time, rapid, appropriate treatment is extremely important. Here, we report a prospective registration of the effect of intravenous (IV) valproate (VPA) on SE/SA in a group of Norwegian patients. **PATIENTS AND METHODS:** Forty-one adult patients (18 males, 23 females) were included in the study. All had previously been unsuccessfully treated with diazepam. For 19, the main SE/SA seizure type was generalized tonic-clonic, while 16 had complex-partial seizures. Six had seizures that were difficult to classify. The treatment protocol recommended 25 mg/kg of VPA loading dose over 30 min, followed by continuous infusion of 100 mg/h for at least 24 h, then per oral administration. If seizures persisted after the loading dose, general anaesthesia (barbiturates/propofol/midazolam) was administered. **RESULTS:** No serious side effects were reported. In 76% of the cases (31 of 41), SE/SA stopped and anaesthesia was not required. Of the patients treated within 3 h, only 5% needed anaesthesia, whereas of those treated after 3–24 h, 38% needed anaesthesia. Of those who waited for more than 24 h before treatment, 60% required anaesthesia. Furthermore, 60% of the patients who needed anaesthesia were given loading doses below 2100 mg. **CONCLUSIONS:** VPA seems to be a safe, effective treatment of SE/SA, but efficacy is dependent on time lapse between symptoms and VPA treatment, and administration of a sufficiently high loading dose.

COMMENTARY

The Veterans Administration collaborative study (VACS) is the largest and most important study, to date, on the treatment of generalized convulsive status epilepticus (GCSE) (1). The investigators compared the safety and efficacy of four commonly prescribed antiepileptic drug (AED) regimens in 384 patients. The regimens included intravenous (IV) lorazepam, phenobarbital, and phenytoin given as monotherapy, and diazepam followed by phenytoin. Overt GCSE remitted in 64.9% randomized to lorazepam, 58.2% treated with phenobarbital, 43.6% of patients randomized to phenytoin, and 55.8% given diazepam followed by phenytoin. A switch to any of the other three treatment arms yielded seizure remission in only 10% of patients whose GCSE persisted after the initial AED trial. Since the publication of that study, other AEDs, not used in the VACS, have been evaluated in the management of status epilepticus (SE). They include IV valproate (VPA), high-dose oral topiramate, and more recently levetiracetam, as oral or IV preparations. IV VPA has been the AED most extensively studied.

Efficacy of IV VPA has been demonstrated in animal models of SE. For example, Martin and Pozo used an in vivo model of SE induced by intrahippocampal application of 4-aminopyridine; IV VPA was administered before or after the induction of SE (2). The intrahippocampal injection of 4-aminopyridine induced continuous epileptic activity without a

clinical component and lasted more than 60 min. IV administration of 400–600 mg/kg VPA over a period of 100 s abolished the SE, and this effect persisted for more than 4 h. Of note, IV administration of 100–300 mg/kg VPA did not abolish previously induced SE, but prevented the appearance of SE when applied before the induction of SE. In contrast, the IV injection of 80 mg/kg phenytoin or carbamazepine did not abolish or prevent SE. In a separate study, Walton and Treiman tested the efficacy of IV VPA in a model of GCSE rats with cortical cobalt lesions; the animals were injected with homocysteine thiolactone to induce secondarily generalized tonic-clonic seizures (3). They found that seizure remission occurred at a median effective dose of 211.9 mg/kg, which yielded a serum concentration of 270 $\mu\text{g/mL}$ at 30 min after the dose was given; all doses were administered intraperitoneally following the second generalized tonic-clonic seizure.

Recently, Trinka as well as Larch and Trinka presented the results of a systematic review of the literature on the efficacy of IV VPA in various forms of SE (4,5). The investigators identified 20 published studies (13 retrospective, 7 prospective) that together involved 533 adults and children. Seizure control was achieved within 20 min of the IV VPA infusion in three-quarters of patients, and the authors concluded that this AED was as effective as phenytoin in resolving SE in patients who had previously failed conventional first-line therapies, such as benzodiazepines. Unfortunately, most of the studies included in the review were uncontrolled trials, leaving open room to question whether the findings might be spurious.

In one of two randomized, open studies carried out thus far on GCSE, 68 patients were assigned to IV VPA or IV

phenytoin, as first line therapies (6). Seizure remission was reached in 66% of patients administered VPA and 42% given phenytoin. Of note, these remission rates were almost identical to those yielded by GABAergic AEDs (e.g., lorazepam, phenobarbital, diazepam) in the VACS. For patients whose seizure activity persisted at the end of the initial AED trial, a switch to the other AED was carried out. Among patients switched to valproic acid, 79% became seizure-free, but this outcome occurred in only 25% of patients switched to phenytoin. Unfortunately, the study was underpowered to demonstrate superiority of VPA over phenytoin, and hence, the difference in efficacy was only suggestive (7). In the second randomized study on GCSE, 40 children with refractory SE were randomized to treatment with either IV VPA or IV diazepam (8). Seizure activity remitted in 80% of children given IV VPA and 85% on IV diazepam. The median time needed to control the refractory SE was significantly shorter with VPA (5 min) than diazepam (17 min).

In the VACS, only 10% of patients whose seizure activity persisted after administration of the initial trial remitted with one of the other three treatment alternatives (1). This low remission rate contrasts with the 79% remission rate found with use of IV VPA in patients who failed to respond to phenytoin (6). Whether the difference is meaningful is yet to be determined, since the VACS did not include IV VPA as one of the treatment arms. Yet, such high success has been reported in other studies in which SE failed to be controlled with benzodiazepines. The present study by Olsen et al. is a case in point: seizure activity stopped in 76% of 41 adults with SE ($n = 21$) or serial seizures ($n = 12$) treated with VPA. This entire group of patients had previously been unsuccessfully treated with IV diazepam. Do these data suggest that IV VPA is more effective than the first-line therapies used in the VACS? Or, is it possible that the therapeutic effect yielded by VPA was the result of an enhanced effect of the prior administration of diazepam. For example, is it possible that 76% of patients whose seizures failed to stop with benzodiazepines remitted with VPA, not only because of the latter's anticonvulsant effect, but also by a positive pharmacodynamic interaction between VPA and diazepam? By the same token, is it possible that the remission of SE with IV VPA in cases of unsuccessful prior trials with IV phenytoin can be explained as well by an increase in the free fraction of phenytoin, caused by its displacement from albumin receptors?

In addition to its successful treatment of GCSE, the efficacy of IV VPA has been observed in trials involving nonconvulsive SE with complex partial seizures, absence status, and in status myoclonicus (4,5), though each of the studies were based on open trials. Despite all of these promising data suggestive of

the efficacy of IV VPA in the treatment of SE, at this point, there are no methodologically sound head-to-head comparison studies to suggest that VPA is superior in efficacy to any other AEDs.

With respect to its safety and tolerability, the profile of IV VPA appears to be very attractive, as it does not have the adverse events encountered with the benzodiazepines, phenobarbital, and phenytoin (8–10). Indeed, IV VPA rarely is associated with cardiovascular adverse events, such as hypotension or arrhythmia, even when administered at high doses with very rapid infusions, and it has not been found to cause respiratory depression. With such a profile, VPA would be the ideal first-line treatment of SE. . .if we only had methodologically sound data to support this indication! Unfortunately, difficulty with getting institutional review board approval to conduct head-to-head comparisons of drugs for SE (at least in the United States) poses significant obstacles to obtaining relevant data.

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