

THE STATUS OF INTRAVENOUS VALPROATE FOR STATUS

Sodium Valproate vs Phenytoin in Status Epilepticus: A Pilot Study. Misra UK, Kalita J, Patel R. *Neurology* 2006;67(2): 340–342. Sixty-eight patients with convulsive status epilepticus (SE) were randomly assigned to two groups to study the efficacy of sodium valproate (VPA) and phenytoin (PHT). Seizures were aborted in 66% in the VPA group and 42% in the PHT group. As a second choice in refractory patients, VPA was effective in 79% and PHT was effective in 25%. The side effects in the two groups did not differ. Sodium valproate may be preferred in convulsive SE because of its higher efficacy.

COMMENTARY

First line treatment for status epilepticus in the United States consists of intravenous (IV) benzodiazepines, usually lorazepam; the treatment protocol is based primarily on the results of the landmark Veterans Affairs Cooperative Status

Epilepticus trial results (1). In that trial, lorazepam was most effective (65% of patients), followed by phenobarbital (58%), diazepam plus phenytoin (56%), and then phenytoin alone (44%; statistically inferior to lorazepam). Another important observation from the trial was that when first line treatment was ineffective (which occurred in 45% of cases), the second agent was rarely effective—only 7% of patients responded to the second agent overall. This finding has led some experts to suggest moving directly to the highly effective and rapidly acting, anesthesia-inducing, continuous infusions (e.g., midazolam or propofol) when lorazepam fails. These continuous infusions can be initiated instead of or simultaneous with loading of the next agent, which is most commonly phenytoin or fosphenytoin (though phenobarbital still remains a reasonable option).

Misra et al. now have performed a useful prospective, randomized, head-to-head clinical trial of IV valproate versus IV phenytoin as first line treatments for convulsive SE in 68 patients of any age (the majority were adults). The study was performed in India and was not blinded. Status epilepticus was appropriately defined as >10 min of seizure activity (continuous or intermittent without return to baseline). Why benzodiazepines were not given first is unclear, but the study design makes the results easier to interpret, even if a bit less applicable to clinical care in the United States. As the initial treatment, valproate (30 mg/kg over 15 min) was superior to phenytoin (18 mg/kg at 50 mg/min), aborting status epilepticus in two-thirds of patients versus 42%, a difference barely reaching statistical significance. If the first medication failed, patients were crossed over to the other. As a second line agent, valproate was markedly superior to phenytoin ($p = 0.004$). About half the patients had recurrence of seizures within 24 h, with seizure freedom nonsignificantly more likely in those who received valproate alone (57%) than phenytoin alone (43%). Adverse effects were similar, but phenytoin was associated with hypotension in two patients (compared to none with valproate) and respiratory depression in two individuals (compared to one on valproate).

Appropriately, an EEG was performed if the patient did not wake up within 1 h after status epilepticus, as these patients are at high risk for nonconvulsive seizures. Information regarding the results of these EEGs or even how many were performed is not provided. However, prior studies have addressed this issue. For example, DeLorenzo et al. studied EEG after convulsive status epilepticus in 164 patients (2). After seemingly successful treatment of convulsive movements, 14% of the patients were in nonconvulsive status epilepticus on EEG and 48% had nonconvulsive seizures on prolonged monitoring—the vast majority with no overt clinical signs. Intermittent and continuous seizures were independently associated with worse outcome, with evidence of a “dose effect”: mortality was 13% if no seizures were found, 32% with intermittent seizures, and 51% when continuous seizures were seen.

The study by Misra et al. is not the first to show the utility of IV valproate for status epilepticus, but it is the first to demonstrate superiority over another commonly used IV antiepileptic drug. A prior retrospective study of IV valproate use in 102 patients in seizure emergencies, many of whom were in status epilepticus, showed success in 86% of patients (defined as cessation of seizures within 15 min and no return over 12 h) (3). Success in the subgroup of 35 patients with status epilepticus was 77%; 29 of those 35 patients had received benzodiazepines prior to valproate. There were no serious side effects reported. Although it is only approved up to a rate of 3 mg/kg/min, IV valproate has been shown to be safe and well tolerated at rapid infusion rates of up to 6 mg/kg/min (allowing a full load in approximately 5 min) (4). It has shown efficacy in multiple types of status epilepticus, in medically unstable elderly patients (5), and in all age groups, including children (6).

As mentioned, in the Veterans Affairs Cooperative Study, IV phenytoin by itself had the lowest success rate. However, it is unknown how valproate would have fared compared to the other study arms (including to the gold standard of lorazepam), because they were not part of the trial. Benzodiazepines should remain the first line treatment for status epilepticus—either IV, nasally, buccally, or rectally. However, when IV benzodiazepines fail, there are many reasonable options: phenytoin, fosphenytoin, midazolam, propofol, phenobarbital, and now IV valproate. It remains to be seen if IV valproate is effective when IV lorazepam has failed, though it appears to be based on the series from Peters and Pohlmann-Eden (3). If a patient is still convulsing after 0.1 mg/kg of lorazepam, proceeding to midazolam or propofol and simultaneously loading a longer-term antiepileptic drug, such as IV phenytoin/fosphenytoin or IV valproate, is a reasonable approach as well. However, a randomized trial of potential treatment options after lorazepam failure is needed. It would have been interesting if Misra and colleagues had included a third arm that evaluated lorazepam as well, though doing so would have required a larger, more costly trial.

Valproate is not without its downside. It can cause coagulopathy as a result of thrombocytopenia (usually dose-related and benign), platelet dysfunction, and hypofibrinogenemia as well as from deficiencies of multiple coagulation factors (e.g., von Willebrand factor, vitamin K-dependent coagulation factors, and factor XIII) (7). It also is associated with hyperammonemic encephalopathy, parkinsonism, and rarely pancreatitis or hepatic failure. Nonetheless, it is quite well tolerated as a rapid IV infusion and is effective for all types of status epilepticus. Now that there is evidence that valproate may be more effective than IV phenytoin for convulsive status epilepticus, it should be confirmed in a larger, double-blinded study, including an evaluation of its efficacy following benzodiazepines.

The study by Misra et al. and other recent studies clearly establish IV valproate as one of the prime players in the treatment of status epilepticus. Time will tell if recently released IV levetiracetam will be similarly effective and well tolerated and where exactly all these agents fit into current treatment algorithms. It certainly is good news to have more IV agents available for status epilepticus and more prospective randomized trials such as this one.

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References

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