A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus (The Veterans Affairs Status Epilepticus Cooperative Study Group)

NEJM 1998 Sept 17; 339 (12): 792-798

At the time of this study, IV treatment options for generalized convulsive status epilepticus (SE) included phenobarbital, phenytoin, diazepam + phenytoin, and lorazepam. However, few trials had studied the efficacy of these medications for SE, and few (if any) had directly compared the efficacy of these medications to one another in terms of SE treatment. Hence, the goal of this study was to compare the efficacy of standard doses of each of these medications for the initial treatment of generalized convulsive SE.

**Experimental Design and Statistics**: This was a double-blind study conducted at 16 VA hospitals and 6 other medical centers. The study enrolled patients with overt generalized convulsive SE[1] or subtle generalized convulsive SE[2] on presentation, and randomly assigned patients to receive initial IV treatment with lorazepam (0.1mg/kg), phenytoin (18mg/kg), phenobarbital (15mg/kg), or diazepam + phenytoin (0.15mg/kg + 18mg/kg). Patients who had been previously treated with a different IV medication and patients in whom seizures had stopped by the time of presentation were excluded (additional exclusion criteria is below)[3]. On presentation, patients were then randomized to 1 of 4 treatment kits (see Table 1), which allowed for quick access to the blinded study drugs, each with the appropriate dose and infusion rate. Kits contained 3 boxes, each with a different medication: the first box was used for initial treatment, and the other 2 contained different study drugs if additional therapy was needed. Following initial treatment, cEEG was started, after which vitals, level of consciousness (LOC), and seizure activity were monitored for 40min. Thereafter, seizure activity and LOC were further monitored for the 12hr study period. The primary outcome was the rate of successful treatment, defined as 1) cessation of clinical and EEG seizure activity at 20min post treatment, and 2) a lack of recurrent seizures from 20 – 60min post treatment. Statistically, subtle and overt SE patients were analyzed separately, via the intention-to-treat principle. If an enrolled patient was later deemed to be without SE (via EEG data) on presentation, they were considered "successfully treated" and were analyzed separately from those with verified SE on presentation. In those with verified SE, Chi-square tests were used to compare the rates of successful treatment, SE recurrence, and ASEs between each study drug.

**Results**: A total of 1705 patients were screened, of which 518 (384 overt, 134 subtle) were eventually used in the verified-SE analyses; 570 patients were initially enrolled but 52 were later found to be without active SE so their data was analyzed but excluded from the verified-SE analyses. Table 2 shows the (expected) differences in baseline patient characteristics between the subtle and overt SE groups, but within each SE group, there were no differences between those randomized to each of the 4 treatment groups. In terms of the primary outcome, the first IV treatment was successful in 55.5% of patients with verified overt SE, but only in 14.9% of patients with verified subtle SE (Fig 1). In the verified overt SE group, lorazepam was statistically more successful than phenytoin when used as the first IV treatment option (main effect of drug: $p = 0.02$); other pairwise comparisons between study drugs were non-significant. In the subtle SE group, there were no differences between any of the study drugs in

[1] Overt SE: 2 or more generalized convulsions w/out return to baseline in between OR continued seizures for >10min

[2] Subtle SE: coma state + ictal discharges on EEG, with or w/out subtle convulsive movements (arm, face or trunk twitching, eye deviation, nystagmus)

[3] Exclusion criteria: age <18, SE other than generalized convulsive, pregnancy, surgical need on presentation, or known contraindications to any of the study drugs

terms of success rate, though all were LESS successful overall than in the overt SE group. Regarding drug ASEs, hypotension and cardiac arrhythmias occurred with equal prevalence after use of all 4 study drugs, though hypotension occurred more often in subtle SE than in overt SE (Table 4). Secondary analyses showed that 11% of patients with overt SE and 20% of patients with subtle SE had SE recurrence in 12hrs, but no differences were found between study drugs. Patients with subtle SE also had poorer, overall outcomes than overt SE: 17% of overt SE vs. 0% of subtle SE patients regained consciousness in 12hrs, and the 30d mortality rate was 64.7% in subtle SE vs. 27% in overt SE.

**Conclusions**: Overall, this study was among the first to show that IV lorazepam was most effective as a first-line, IV therapy for convulsive, generalized SE. Notably, lorazepam was only statistically more successful than phenytoin, suggesting that the other study drugs used here (phenobarbital, diazepam + phenytoin) were also good options[4]. Nonetheless, this study generally contributed to our current practice of using IV lorazepam first, for SE and initial seizure management. Further, the secondary analyses in this trial highlighted the severity of subtle (i.e., nonconvulsive) SE, given the high mortality rate and low likelihood of early return to consciousness in this group. In the end, however, given the somewhat low success rate of the study drugs, overall, for SE cessation, the study authors noted the need for better treatment, beyond that of IV benzodiazepines, for initial treatment of SE.

Summary created by Elaine Sinclair, D.O.

[4] The study authors suggested that the slow infusion rate of phenytoin (>30min) and the operational criterion for success of treatment (no SE recurrence in 20min) could have contributed to the observed lorazepam vs. phenytoin difference here (Table 3), though they also note that infusion rates for the other study drugs (phenobarb + diazepam/phenytoin) were close to or beyond the 20min time point as well, and were no different in efficacy from lorazepam.