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Rational Polytherapy in the Treatment of Acute Seizures and Status Epilepticus

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Monotherapy is widely accepted as the best option for treatment of epilepsy, and controlled studies of the treatment of status epilepticus (SE) have shown lorazepam monotherapy to be as effective as any treatment tested (Treiman et al, 1998). However, the major reasons for preferring monotherapy in the treatment of chronic epilepsy, such as minimizing lifelong exposure to potentially toxic drugs, may not apply to SE, an acute, life-threatening event of limited duration. There is a paucity of experimental or clinical evidence supporting the superiority of monotherapy in the treatment of acute seizures and SE. There is also no consensus on the criteria which allow comparisons between the benefits and adverse effects of mono- and polytherapy.

Recent studies have shown that seizure-induced trafficking of synaptic GABA and glutamate receptors causes both a reduction of GABAergic inhibition and an increase in glutamatergic excitation in hippocampus during SE (Naylor et al 2005, Goodkin et al 2008). This might suggest that combination therapy aimed at correcting the consequences of both changes may be more effective than monotherapy targeting only one of those pathophysiological mechanisms (Chen & Wasterlain, 2006). In the present study, we propose the use of a key measure of drug toxicity as the standard to compare the effect of a single drug to those of two- or three-drug combinations. This standard could vary with the therapeutic situation. For example, in developing countries where fully equipped intensive care units are in short supply, respiratory depression might be a key measure of toxicity for the safe treatment of SE, while in a well-equipped ICU, respiratory depression might not be considered a key factor, but major depression of systolic blood pressure would be the key measure of toxicity.

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Our studies used a model of severe SE induced by cholinergic agents (Tetz et al 2006), and designed to mimic the effects of $1.2 \times \text{LD}_{50}$ dose of the nerve agent soman. Because this model might apply to battlefield or terrorism situations where the victims' mobility is important, we selected the ability to move about and to retain consciousness as our key measures of drug toxicity. Gait ataxia, loss of the righting reflex, abolition of response to tail pinch, and loss of the corneal reflex were used to measure drug toxicity, summed up over the first hour of exposure in a "toxicity score". Outcome measures were termination of SE, measured by the number of post-treatment seizures, the time between treatment and the first sixty-second interval free of electrographic seizures, the Hjorth number (a rough measure of seizure severity), the time needed for EEG power to decline to twice baseline amplitude, and the duration of SE. Secondary measures were the severity of hippocampal neuronal injury 24 hours after induction of SE and the frequency of spontaneous recurrent seizures recorded at least 6 weeks after SE. Our treatment was designed to counteract the loss of inhibition due to internalization of synaptic GABAA receptors, by allosterically stimulating GABAA receptors with benzodiazepines. We added a drug which enhanced inhibition at a non-GABA site, since GABA agonists can only partially restore GABA inhibition in this model. Finally, we tried to reduce glutamatergic excitation due to an increased number of synaptic NMDA receptors by treating with NMDA antagonists. We administered treatment intraperitoneally after the second convulsive seizure, since preliminary experiments showed that by that time (approximately 20 min. after injection) benzodiazepine pharmacoresistance had developed.

Benzodiazepine monotherapy reduced mortality from 52% to 7% (5 mg/kg diazepam) or less (10-20 mg/kg) but did not stop seizures even at a dose of 20 mg/kg (Dz20), which induced a deep coma. The number of post-treatment seizures was 100 ± 7 in sham-injected controls and 100 ± 8 after 20 mg/kg DZ (N.S.). Monotherapy with ketamine 10 mg/kg (K), valproate 30 mg/kg (V), brivaracetam 10 mg/kg (Brv), diazepam 1, 5 or 10 mg/kg (Dz1, SDz5, or Dz10), and other antiepileptic drugs also failed to stop SE. Combinations of diazepam (1 mg/kg) with ketamine (10 mg/kg) + valproate (30 mg/kg) (Dz1 + K + V), reduced the number of post-treatment seizures to 8 ± 2 ($p < 0.001$ compared to Dz or C) while causing mild ataxia and preserving the righting reflex (toxicity score 1 ± 0.4). Combination of diazepam (1 mg/kg) with ketamine (10 mg/kg) + brivaracetam (10 mg/kg) (Dz1 + K + Brv), reduced the number of post-treatment seizures to 8 ± 4 ($p < 0.01$ compared to DZ or C). Dz1 + K + V caused mild ataxia and preserved the righting reflex (toxicity score 1 ± 0.4), and Dz1 + K + Brv had similar effects (toxicity score 0.8 ± 0.2), while DZ20 severely impaired locomotion and the righting reflex (toxicity score 11.2 ± 0.9). Some two-drug combinations were also significantly more effective than monotherapy in this model. Synergism between drugs was strongly suggested by several methods.

These results suggest that polytherapy can be more effective and less toxic than monotherapy in the treatment of cholinergic SE, and that the optimal therapy of SE and acute seizures may be based on different principles than that of chronic epilepsy.

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References

- Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. *Lancet Neurol.* 2006; 5:246–56. [PubMed: 16488380]
- Goodkin HP, Joshi S, Koshemyakin M, Kapur J. Impact of receptor changes on treatment of status epilepticus. *J Neurosci.* 2008; 28:2527–38. [PubMed: 18322097]
- Naylor DE, Liu H, Wasterlain CG. Trafficking of GABA_A receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. *J Neurosci.* 2005; 25:7724–33. [PubMed: 16120773]
- Tetz LM, Rezk PE, Ratcliffe RH, Gordon RK, Steele KE, Nambiar MP. Development of a rat pilocarpine model of seizure/status epilepticus that mimics chemical warfare nerve agent exposure. *Toxicol Ind Health.* 2006; 22:255–66. [PubMed: 16924957]
- Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, Handforth A, Faught E, Calabrese VP, Uthman BM, Ramsay RE, Mamdani MB. A comparison of four treatments for generalized convulsive status epilepticus: Veterans Affairs Status Epilepticus Cooperative Study Group. *New Engl J Med.* 1998; 339:792–98. [PubMed: 9738086]