

CAN THE LONG-TERM OUTCOME AFTER STATUS EPILEPTICUS BE MODIFIED?

Phenobarbital and MK-801, but Not Phenytoin, Improve the Long-Term Outcome of Status Epilepticus

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To examine the effect of therapy on status epilepticus (SE) acutely and on long-term outcome, we compared three drugs with three different mechanisms. Phenobarbital, MK-801, and phenytoin were administered at 1, 2, and 4 hours after initiation of limbic status epilepticus by “continuous” hippocampal stimulation in rats. We evaluated the effects of these drugs on the course of SE and the subsequent development of chronic epilepsy. Phenobarbital and MK-801 were superior to phenytoin in suppressing SE and in preventing chronic epilepsy. There was no benefit if treatment was given 2 hours after the initiation of SE. Phenobarbital was most effective in suppressing electrographic seizure activity, but MK-801 had a slightly wider window for the prevention of chronic epilepsy. Early treatment, rather than electrographic suppression of SE, correlated with prevention of chronic epilepsy. This study shows that the drugs administered, which have different mechanisms of action, have clear differences in altering the outcomes. The findings suggest that studies of SE treatment should examine the effect of therapy on SE itself, as well as the long-term benefits of each treatment. The use of N-methyl-D-aspartate receptor antagonists should be considered early in the treatment of SE.

Seizure-Induced Memory Impairment is Reduced by Choline Supplementation Before or After Status Epilepticus

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Prenatal choline supplementation can protect rats against cognitive deficits induced by status epilepticus induced by the cholinergic agent pilocarpine [J. Neurosci. 20 (2000) 1]. In the present day, we have extended this novel finding by investigating the effects of pre- and postnatal choline supplementation in memory deficits associated with status epilepticus induced with kainic acid (KA). In the first experiment pregnant rats received a normal, choline-supplemented, or choline deficient diet starting on the 11th day of gestation and continuing until postnatal (P) 7. At P42, rats were given a convulsant dosage of KA. Two weeks following the KA-induced status epilepticus rats underwent testing of visual-spatial memory using the Morris water maze test. Rats receiving supplemental choline performed better in the water maze than the deficient and control groups. Moreover, the activity of hippocampal choline acetyltransferase was 18% lower in the choline deficient animals as compared with the other two groups. In the second experiment we administered KA to P35 rats that had been given a normal diet. Following the status epilepticus the rats were given a choline-supplemented or control diet for 4 weeks and then tested in the water maze. Rats receiving choline supplementation performed far better than rats receiving a regular diet. This study demonstrates that choline supplementation prior to or following KA-induced status epilepticus can protect rats from memory deficits induced by status epilepticus.

COMMENTARY

Status epilepticus (SE) is a neurological emergency with clinical outcome inversely related to the duration of the condition. Many studies have focused on the ability of pharmacological interventions to terminate SE promptly so as to minimize morbidity and mortality. The two articles highlighted here address two other issues of considerable interest. Prasad et al. examine the ability of several anticonvulsant interventions to influence one important adverse long-term outcome of SE—the development of chronic spontaneous sei-

zures. Holmes et al. address the novel concept of a *post hoc* treatment of SE with a nutritional supplement, choline, to improve the cognitive outcome.

Prasad et al. have employed three pharmacologically distinctive treatments in a model of nonpharmacologically-induced limbic SE. Phenobarbital (a GABA_A receptor modulator), phenytoin (a sodium channel antagonist) or MK-801 (an NMDA receptor antagonist) was administered at 1, 2, and 4 hours after initiation of "continuous" hippocampal stimulation. As observed previously, MK-801 was superior to the other treatments in terminating established SE. In the early stages of SE, however, phenobarbital appeared superior to both MK-801 and phenytoin. The best outcome in terms of the prevention of chronic epilepsy was achieved by early (1 h) intervention with phenobarbital or MK-801, with the latter quite effective in its antiepileptogenic efficacy even when used at 2 h into SE. Further, MK-801 was extremely effective as an antiepileptogenic compound even when it was not effective in suppressing electrographic SE. In this model, phenytoin fared the worst both in terms of acute effectiveness and long-term consequences.

These data raise several important issues. It would seem that further studies are needed to determine if phenobarbital is better in humans than phenytoin as initial treatment of SE. Indeed, two clinical studies cited in the article suggest that phenobarbital may be underutilized in the acute treatment of SE. Readers may also view the present animal data in the light of the classic human study by Temkin et al. (1) in which chronic treatment with phenytoin was also not beneficial in the prevention of post-traumatic epilepsy. Is it possible that current practice overvalues phenytoin? Another important topic for further study pertains to the role of these agents for SE in the immature brain. Painter et al. (2) found both phenobarbital and phenytoin to possess shortcomings in addressing neonatal seizures acutely.

The study by Holmes et al. is a novel journey along a road

less traveled: *post-hoc* treatment after SE to minimize long-term morbidity. Using kainic acid as the provocateur for SE and employing the Morris water maze to assess visuo-spatial learning and memory four weeks after SE, the authors describe significant protection from seizure-induced deficits by choline supplementation, even when administered after the episode of SE. The mechanisms for these effects are not known, although one figure in the article demonstrates discernible neuroprotection from choline supplementation in the hippocampus. It is tempting to compare these data to the *in vitro* study of Alkondon et al. (3), who have shown that choline is a good agonist at nicotinic acetylcholine receptors (nAChR) containing the $\alpha 7$ subunit. Acting at these receptors, choline stimulates action potential firing in interneurons, resulting in GABA release which can have a neuroprotective effect. Activation of nAChR by choline may also have a beneficial impact on cognitive function. Regardless of the mechanisms, the possibility of being able to minimize long-term morbidity from SE by *post hoc* treatment is of great interest. Given the rather benign nature of choline treatment, its potential role in modifying the cognitive consequences of SE deserves further evaluation.

References

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