

RESPONSIVENESS OF STATUS EPILEPTICUS TO TREATMENT WITH DIAZEPAM DECREASES RAPIDLY AS SEIZURE DURATION INCREASES

Characterization of Pharmacoresistance to Benzodiazepines in the Rat Li-pilocarpine Model of Status Epilepticus

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Status epilepticus is usually initially treated with a benzodiazepine (BZD) such as diazepam (DZP). During prolonged seizures, however, patients often lose their sensitivity to BZDs, thus developing pharmacoresistant seizures. In rats, administration of LiCl followed 20 to 24 hours later by pilocarpine induces a continuous, self-sustained, and reproducible form of status epilepticus that can be terminated with DZP when it is administered soon after the pilocarpine injection. However, when administered after a 45-minute delay, DZP is less effective. Previous findings suggested that the development of pharmacoresistance is related to the stage of status epilepticus. In this study, we characterized the seizure stage dependence of DZP pharmacoresistance. After administration of different doses of DZP at varying time intervals after specific behaviorally and electrographically defined seizure stages, stage-, time-, and dose-dependent pharmacoresistance to DZP developed. We also studied two other antiepileptic drugs (AEDs) commonly used in the treatment of status epilepticus, phenobarbital (PB) and phenytoin (PHT). Consistent with previous studies, our results indicated a similar relation between stage, time, and dose for PB, but not for PHT. Our data are consistent with rapid modulation of γ -aminobutyric acid subtype A (GABA_A) receptors during status epilepticus that may result in pharmacoresistance to AEDs that enhance GABA_A receptor-mediated inhibition.

(BZDs) are currently considered the drugs of choice for initial treatment of SE (1). Despite their effectiveness, at least 35% of patients with generalized convulsive SE are refractory to BZDs (2). Refractoriness of SE to therapy may relate to the etiology. For example, postanoxic SE is more refractory to treatment than anticonvulsant or alcohol-withdrawal SE. In addition to etiology, it is a common clinical observation that the likelihood of a patient responding to first-line therapy declines as the time between the onset of the seizure and the onset of treatment initiation increases (3). This observation was supported by the prospective, randomized Veterans Administration cooperative study of the initial treatment of SE. Only 7% to 25% of patients in subtle SE, who were enrolled 5.2 hours after onset, responded to initial treatment, whereas 43% to 65% of patients in overt SE, who were enrolled 2.8 hours after onset, responded to initial therapy.

Walton and Treiman (4) first demonstrated development of refractoriness to BZDs in an experimental model of SE. Diazepam (DZP) stopped all seizures produced by injection of lithium followed by pilocarpine administered shortly after the onset. However, it was effective in only 17% of rats after they had prolonged SE. One subsequent study demonstrated that with passage of time, there was a substantial reduction of DZP potency for termination of the seizures (5). However, the precise time course of development of refractoriness to BZDs during SE has not been delineated in the past, and this study of Jones et al. focuses on this issue.

In the first set of experiments, the BZD DZP was given 10, 20, 30, or 45 minutes after the injection of pilocarpine to adolescent rats pretreated with lithium. Confirming the prior observation, a 10-fold increase in the dose of DZP was required to terminate behavioral seizures observed after the injection of pilocarpine in 50% of animals at 45 minutes as compared to 10 minutes. At the intermediate time points, termination of behavioral changes and recovery of normal function did not appear to be dose dependent.

The development of pharmacoresistance to BZDs was characterized further by timing DZP administration to a clinical seizure stage [onset of forelimb clonus (seizure stage S3 as defined by Racine (6)) or to an ictal electrographic stage (continuous 3- to 4-Hz spike-wave activity; electrographic equiva-

COMMENTARY

Status epilepticus (SE) is neurologic emergency that requires prompt recognition and treatment. Benzodiazepines

lent to S3 in this study). When DZP was administered at the onset of S3, clinical seizure termination and eventual recovery of normal function was observed to occur in a dose-dependent fashion ($ED_{50} = 1.6$ mg/kg). However, when administered 10 minutes after the onset of S3, clinical seizure termination and eventual recovery of normal function within a 3-hour interval was not observed in more than 90% of the animals despite DZP doses of 20 mg/kg. Comparable findings were observed when DZP dosing was based on the electrographic equivalent of S3. In the final set of experiments, similar experiments were performed by using phenobarbital (PB) and phenytoin (PHT). Like DZP, PB was efficacious when administered before or at the onset of S3 but not when administered 10 minutes after onset of S3. In contrast, PHT was not effective at any time point.

In summary, this study demonstrates that in the lithium-pilocarpine model of SE, the development of pharmacoresistance to the GABA_A-receptor agonists DZP and PB occurs rapidly after the onset of forelimb clonus and ictal spike-wave activity. How pharmacoresistance to BZDs develops is not known. Future investigations designed to elucidate the mechanism should concentrate on the cellular (7) and functional anatomic (8) changes that occur at this time.

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