New Data Suggest that Discontinuation of Status Epilepticus Is Not Necessary for Antiepileptogenic Effect in Immature Brain

Treatment of Experimental Status Epilepticus in Immature Rats: Dissociation between Anticonvulsant and Antiepileptogenic Effects

Suchomelova L, Baldwin RA, Kubova H, Thompson KW, Sankar R, Wasterlain CG

Pediatr Res 2006;59:237–243

We studied the effects of treating status epilepticus (SE) induced by lithium and pilocarpine at postnatal day 15 (P15) or 28 (P28), on the severity of acute SE and of SE-induced epileptogenesis. Rats received topiramate (10 or 50 mg/kg, IP) or diazepam (5 mg/kg, IP) 20, 40 or 70 min after pilocarpine, and three months after SE 24-h video/EEG recordings were obtained for one (P28) or two weeks (P15) continuously.

In P15 rats, topiramate did not modify the course of SE, yet treatment at 20 or 40 min completely prevented the development of spontaneous recurrent seizures (SRS) while later treatment (70 min) was partially effective in reducing the severity and frequency of SRS. Diazepam was effective against acute SE at all time points tested. Early (20 min) but not late treatment with diazepam had the effect of reducing the frequency and severity of SRS.

In P28 rats, both drugs reduced the cumulative seizure time. Early treatment (20 min) with either drug reduced the incidence of chronic epilepsy. Late treatment (40/70 min) did not alter the incidence of SRS, but decreased their frequency. This study demonstrates that, in the treatment of SE, anticonvulsant and antiepileptogenic effects can be dissociated in a development-specific manner: topiramate was antiepileptogenic without being an effective anticonvulsant in P15 animals at the doses tested. Diazepam, on the other hand, was a better anticonvulsant than an antiepileptogenic agent in the P15 animals at the dose tested. Such effects were not seen in the older animals.

COMMENTARY

Recent studies aimed at developing antiepileptogenic compounds have used models in which epileptogenesis is induced by status epilepticus (SE). Advantages of using SE as a trigger for the epileptogenic process are that: (i) a large majority of rats develop epilepsy; (ii) the epileptogenic period is relatively short, which reduces the duration of laborious video-EEG follow-up; and (iii) most of the molecular and cellular understanding of the mechanism of epileptogenesis comes from SE models. During preclinical drug trials, a major problem with using SE models has been distinguishing the antiepileptic effect from the antiepileptogenic effect of a compound—a process that is particularly difficult if the antiepileptic compound is administered within 24 hours after induction of SE. As studies with adult rats have shown, discontinuation or alleviation of SE reduces the risk and ameliorates the clinical symptomatology of epilepsy (1). A true antiepileptogenic compound is expected to modify the molecular and cellular cascades that underlie circuitry reorganization that leads to epilepsy—not simply to stop the initiation of these cascades by suppressing SE.

Epilepsy Currents, Vol. 6, No. 5 (September/October) 2006 pp. 170–172
Blackwell Publishing, Inc.

In the present study, Suchomelova and coworkers triggered SE with lithium–pilocarpine in two rat groups on postnatal day 15 (P15) and P28. Considering that SE activity appeared about 8 minutes after pilocarpine administration in both the P15 and P28 groups, the animals had been in SE for 12, 32, or 62 minutes, respectively, before initiation of treatment at 20, 40, or 70 minutes. Treatment regimens included: (i) atropine monotherapy (10 mg/kg), which should eliminate the receptor-mediated effects of pilocarpine (i.e., SE would continue only if it had become self-sustained); (ii) topiramate (10 mg/kg) plus atropine (10 mg/kg) combination therapy; or (iii) diazepam (5 mg/kg) plus atropine (10 mg/kg) combination therapy. Assessed 3 months later using video-EEG monitoring, the basic observation was that topiramate did not affect the duration or severity of SE in the P15 group but almost completely prevented the development of epilepsy, whereas even though diazepam efficiently suppressed SE activity, it had a milder effect on epileptogenesis. The authors suggest that the "anticonvulsant and antiepileptogenic properties of a drug can be dissociated, and that the extent of this dissociation can vary with the degree of brain maturation." However, it is important to ask whether this is the only way of interpreting the data presented.

Does the timing of initiation of SE treatment influence the risk of epileptogenesis? Studies involving adult and juvenile rats

(including this study) have shown that the duration of SE should be minimized to reduce the risk of epileptogenesis and other unfavorable outcomes. This effect is obtained by initiating treatment as soon as possible, by rapid discontinuation of SE, or by a combination of both these methods. The present study confirms previous observations that the percentage of rats that developed epilepsy is lower if treatment is started at 20 to 40 minutes rather than at 70 minutes after induction of SE. This outcome was particularly clear in both the P15 and P28 diazepam-treated animals. The trend was also visible in the topiramate-treated rats. The interpretation of data is complicated by the lack of information regarding whether the P15 rats, who were given atropine monotherapy at 20 or 40 minutes after pilocarpine administration, developed epilepsy. An earlier study by the same group showed that only 3 of 11 (27%) rats that underwent lithium–pilocarpine-induced SE at 2 weeks of age without atropine treatment developed spontaneous seizures when observed for at least 4 months (2). Early administration of atropine could be expected to reduce the risk of epileptogenesis even further. This hypothesis is supported by the data shown here that none of the rats in the 20-minute or 40-minute topiramate+atropine combination therapy groups developed epilepsy. Thus, it is unclear whether the study paradigm actually can be used to assess antiepileptogenic effects, because differences in these effects would be detected only if the treatment increased the risk of epileptogenesis.

Are the delay to reach burst suppression or the discontinuation of SE important factors in the risk of epileptogenesis? In the treatment of SE, the goal is to discontinue SE as soon as possible in order to reduce mortality and improve outcome (3). According to findings of Suchomelova and coworkers, latency to seizure interruption after administering topiramate+atropine combination therapy in the 20-, 40-, and 70-minute P15 groups was 75 minutes, 47 minutes, and 34 minutes, respectively. The authors concluded that topiramate+atropine combination therapy did not discontinue SE in the P15 group. Another interpretation could be that the earlier the treatment was given, the longer it took to stop the SE. Again, it is difficult to interpret the efficacy of topiramate+atropine combination therapy because no data are presented on the effects of atropine monotherapy in the 20-minute or 40-minute groups. Within a 3-month follow-up, however, none of the rats in the 20-minute or 40-minute topiramate+atropine groups developed epilepsy, while 14% of the rats in the 70-minute group did. Diazepam+atropine combination therapy discontinued seizure activity in about 13 minutes; among the P15 animals, epilepsy occurred in 17% of the 20-minute group, 33% of the 40-minute group, and 50% of the 70-minute group. Do these data indicate that rapid suppression of seizure activity with diazepam actually increases the risk of epileptogenesis in P15 rats, as compared to the topiramate group in which SE was discontinued more slowly (present study) or to the untreated group in which the epilepsy developed in 27% of rats (2)?

Is it choice of treatment rather than the duration of SE that is more important when assessing the risk of epileptogenesis? It is interesting to note that the time in seizure for the P15 70-minute atropine monotherapy group was 196 minutes and the total duration of SE was 17.6 hours; for the topiramate+atropine combination therapy group, the time in seizure was 173 minutes and total duration of SE was 13.6 hours; while in the diazepam+atropine group, the time in seizure was only 76 minutes and the duration 4.1 hours. The percentage of rats that developed epilepsy was 75%, 14%, and 50%, respectively. Thus, the severity or duration of SE is not as important as the treatment chosen in determining the risk of epileptogenesis. In other words, as long as a single shot of topiramate+atropine is administered within an hour after the beginning of SE, the risk of epileptogenesis will reduce from 75% to 14%, even though it will not substantially alleviate SE. Choosing diazepam to efficiently stop SE (at least temporarily), however, does not reduce the risk of epileptogenesis remarkably (from 75% to 50%). The authors note that increasing the dose of topiramate from 10 mg/kg to 50 mg/kg will eliminate the beneficial antiepileptogenic effect, which makes it even more complicated to understand what topiramate's mechanism of action might be in the P15 brain. It remains to be determined whether the recent observations that topiramate has multiple molecular sites of action would provide an answer to this issue (4). Finally, all treatments in both age groups had a clear disease-modifying effect of reducing the weekly seizure frequency—independent of whether the treatment was antiepileptogenic or not. Such dissociation between antiepileptogenesis and disease modification has previously been reported after administering the proconvulsant, atipamezole, which is an α_2-antagonist that has no antiepileptogenic effect but substantially reduces seizure frequency (5). Therefore, the Suchomelova et al. findings beg the question of whether suppression of seizure activity in the immature brain is as beneficial as previously thought in decreasing the risk of epileptogenesis after SE (6).

Is the electrographic assessment of the severity and duration of SE optimized? One of the major challenges in performing preclinical studies using SE as a trigger for epileptogenesis is how best to define and quantify different kinds of electrographic activity that occur during SE. Previously, various investigators have tried to develop easily measurable markers for EEG of adult rats to quantify the severity and duration of SE (5,7). The following markers also were used by Suchomelova and colleagues:

- Latency to seizure interruption (i.e., time from drug administration to at least a 1-minute interruption of continuous polyspike or spike-and-wave activity)

- Cumulative seizure time (i.e., duration of seizure time after drug administration, subtracting interictal time)
- Number of seizures (i.e., a discharge lasting at least 3 seconds, with a mean frequency of at least 3 Hz, and an amplitude 2.7 times higher than baseline)
- Duration of SE (i.e., time from the onset of SE to the end of the last seizure, including interictal time)
- Total seizure time (i.e., total time spent in seizures from the beginning of SE, minus interictal time)
- Spike frequency (i.e., number of spikes per hour)

It is anticipated that these markers could provide unbiased criteria to determine whether the benefits of a compound stemmed from an antiepileptogenic effect or simply from amelioration of the SE itself. The analysis relies on the assumption that dividing the electrographic SE activity into "seizures" and remaining "interictal time" will derive the duration and severity of SE. There are some hidden caveats to this theory. The duration of SE is defined as an interval between the first and last seizure. However, the distribution of individual seizures within this time period can vary substantially. For example, the drug (e.g., diazepam) can discontinue the high-amplitude and frequency discharges (seizures) for many hours but then suddenly one seizure occurs, and consequently, the duration of SE becomes substantially prolonged as a result of that one seizure. Furthermore, the duration of individual seizures can vary and having no data available about the association between epileptogenicity and seizure duration, it is difficult to know whether variable effects of different treatments could relate to altered epileptogenicity of the EEG. The number of spikes over time likely is the best marker to detect the antiepileptic effects of a compound on seizure activity during SE, which unfortunately was not presented in the study by Suchomelova et al.

It will be necessary to continue to analyze the spectrum of various patterns of electrical activity during SE to identify the best surrogate markers to predict epileptogenesis and determine the effects of candidate antiepileptogenic treatments. It will be important to know whether the same criteria can be applied across different age groups. Furthermore, development and use of markers is important in order to avoid missing ameliorating effects of compounds on SE activity, as happens with current parameters.

In conclusion, Suchomelova and colleagues present unexpected data that challenge the old thinking that electrical activity during SE must be suppressed to modify the epileptogenic process, particularly in immature brain. Further studies, including a detailed analysis of effects of topiramate+atropine combination therapy on electrical activity of the brain during SE are necessary to confirm this surprising finding to assure that the change in old dogma does not occur prematurely. Considering that the neurobiological basis of epileptogenesis shares many similarities with the recovery process after brain trauma, unexpected data are more than welcome to facilitate conceptualization of novel research and treatment strategies for epileptogenesis in immature and mature brain.

by Asla Pitkänen, MD, PhD, DSc

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