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The Acute and Chronic Effects of the Novel Anticonvulsant Lacosamide in an Experimental Model of Status Epilepticus

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Abstract

The effective management of status epilepticus (SE) continues to be a therapeutic challenge. The aim of this study was to investigate the efficacy of lacosamide treatment in an experimental model of self-sustaining SE.

Rats were treated with lacosamide (3, 10, 30 or 50 mg/kg) either 10 minutes (early treatment) or 40 minutes (late treatment) after the initiation of perforant path stimulation. Early lacosamide treatment significantly and dose-dependently reduced acute SE seizure activity; late treatment showed only a non-significant trend towards reduced seizure activity. Early lacosamide treatment also dose-dependently reduced the number of spontaneous recurrent seizures following a 6-week waiting period, with 70% reduction at the highest dose tested (50 mg/kg); there was also a significant reduction in the number of spikes and the cumulative time spent in seizures. Late treatment with high-dose lacosamide (30–50 mg/kg) reduced the number of animals that developed spontaneous recurrent seizures (33% vs 100% in controls, $P < 0.05$), but did not significantly reduce seizure severity or frequency in rats that developed spontaneous recurrent seizures..

The results presented here suggest that lacosamide deserves investigation for the clinical treatment of SE. Potential for disease modification in this rat model of self-sustaining SE will require further studies.

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Keywords

Antiepileptic Drug; Lacosamide; Status Epilepticus; Perforant Pathway Stimulation; Spontaneous Recurrent Seizures; Rat

1. Introduction

Recent population-based studies indicate that SE still carries an acute mortality of 27% in adults, and there is a general consensus that standard drugs used to treat SE are unsatisfactory. Clinically, intravenous lorazepam or diazepam alone or paired with phenytoin or fosphenytoin is the standard first-line therapy for SE (Treiman et al., 1998; Trinka, 2007), but response to treatment rapidly declines with increasing seizure duration (Mazarati et al., 1998; Treiman et al., 1998). Furthermore, the use of phenytoin and fosphenytoin has been associated with untoward side effects, such as arrhythmias and hypotension, particularly in patients over the age of 40 (Trinka, 2007). Given the persistently high mortality and morbidity rates of patients with SE (deLorenzo et al., 2009), especially those with refractory SE (Mayer et al., 2002; Treiman et al., 1998), alternative treatments are needed to attenuate the clinical complications and to effectively terminate SE with minimal risk for adverse events.

Lacosamide ([R]-2-acetamido-*N*-benzyl-3-methoxypropionamide) is a unique functionalized amino acid that was specifically synthesized for use as an AED (Beyreuther et al., 2007; Stöhr et al., 2007). Lacosamide has received EMEA marketing authorization and FDA approval for use as adjunctive treatment for partial-onset seizures in adults. Lacosamide is available in an injectable form, but is not currently approved for the treatment of SE. The antiseizure effects of lacosamide were established in multiple rodent models for epilepsy and showed that lacosamide prevented seizure spread (maximal electroshock test), protected against sound-induced seizures (Frings audiogenic seizures), was effective in controlling treatment-resistant seizures (6-Hz psychomotor seizure test), and attenuated the effects of intravenous infusion of pentylenetetrazole. In the 6-Hz model, lacosamide also exhibited synergism in isobolographic analysis with several AEDs, including carbamazepine and levetiracetam (Beyreuther et al., 2007). Additionally, lacosamide limited complex partial seizures following hippocampal kindling (Stöhr et al., 2007) and was also effective in retarding development of amygdala kindling, indicative of a putative antiepileptogenic effect (Brandt et al., 2006).

In electrophysiologic studies, lacosamide selectively enhanced voltage-gated sodium channel slow inactivation without affecting other biophysical properties of the sodium channel, including rate of recovery (Errington et al., 2008; Sheets et al., 2008). This presumed mechanism of action differs from other commonly used AEDs (such as oxcarbazepine, lamotrigine, carbamazepine and phenytoin) that act on fast inactivation of sodium channels. The novel electrophysiologic effects combined with an established efficacy in animal models of epilepsy make lacosamide an interesting candidate for study in the treatment of SE.

Electrical stimulation of the rodent perforant path, (the largest glutamatergic input from entorhinal cortex to hippocampus) has been used to investigate numerous AEDs as potential therapeutic options for SE, such as felbamate, fluorofelbamate, topiramate, lamotrigine, and levetiracetam (Fisher et al., 2004; Gibbs et al., 2006; Gibbs and Cock, 2007; Halonen et al., 2001; Mazarati et al., 1998; Mazarati et al., 2000; Mazarati et al., 2004). The electrical stimulation model developed in our laboratory (Mazarati et al., 1998) uses brief, intermittent stimulation of the perforant path to produce self-sustaining SE (SSSE). Intermittent

stimulation for 30 minutes in unmedicated awake rats induces SSSE that lasts approximately 16 hours without further stimulation, becomes refractory to the standard SE treatments, diazepam and phenytoin, and results in quantifiable neuronal damage and chronic epilepsy in long-term survivors. Thus, this model can also serve as a means to study neuroprotective and antiepileptogenic drug properties. Using this SSSE model, we have previously shown that pretreatment with levetiracetam reduces or prevents self-sustaining seizures, and that treatment with levetiracetam during SSSE reduces or terminates seizures and can enhance the effects of diazepam at low concentrations (Mazarati et al., 2004). Given the importance of identifying new treatments for SE coupled with the promising effects of lacosamide in other seizure models, we investigated the effects of lacosamide in the perforant path stimulation model for SSSE.

2. Methods

2.1 Animals

Male Wistar rats (Simonsen labs, Gilroy, CA, 260g – 280g at the beginning of the study) were housed in an animal facility for 7 – 10 days for habituation prior to experimental testing. The animals were housed individually in cages maintained at a temperature of 22 ± 2 °C, and with facility lighting turned on from 6 am to 6 pm everyday. Rats were allowed free access to Purina rat chow pellets and water. All procedures followed institutional guidelines and were approved by the institutional review board of the VA Greater Los Angeles Health Care System.

2.2 Surgical Implantation of Stimulating and Recording Electrodes

Under isoflurane (3%, VET SUPPLY GLOBAL CO., LTD, Egypt) anesthesia, animals were placed into a stereotaxic frame. The scalp was shaved, cleaned with alcohol and an incision from between the eyes to ear level was made to expose the skull. Using coordinates from the Paxino and Watson rat atlas, burr holes were made in the skull at 0.5 mm anterior and 4.5 left of lambda for the bipolar stimulating electrode into the angular bundle of the left perforant path and 3 mm posterior and 2.5 mm left to bregma for the bipolar recording electrode into the ipsilateral dentate gyrus.

The electrodes (Plastics One MS333/3-A and MS303/2) were scraped to remove the insulating layer before being implanted at a depth of 3.5 mm to 4 mm from the brain surface, optimized by finding the maximal population spike evoked from the dentate gyrus following stimulation of the perforant path. The electrodes were connected to skull screws placed to the left and right of the midline and 1 – 2 mm anterior to lambda, and connected to the leads from a radio telemetry transmitter (Data Science International TA10EA-F20) that was implanted subcutaneously on the animal's back. The scalp was then sutured, and immediately after surgery the animal was injected subcutaneously with buprenorphine (0.05 mg/kg) to relieve pain and enrofloxacin (5 mg/kg) to prevent infection. Each animal was allowed to recover from surgery for 13 – 15 days.

2.3 Induction of self-sustaining status epilepticus (SSSE) and administration of lacosamide

SSSE was induced as previously described (Mazarati et al., 1998). Briefly, perforant path stimulation (PPS) was delivered for 30 minutes (Grass stimulator model 8800) with the following parameters: 10 s, 20 Hz trains of 1 ms, 30 V pulses delivered every minute, together with continuous 2 Hz stimulation with the same parameters.

Lacosamide (3 – 50 mg/kg, a generous gift from Schwarz Biosciences GmbH.) dissolved in 10% DMSO was injected intraperitoneally; control animals were injected with vehicle. A

total of 6 animals per treatment group were used. Each rat was treated with a single dose of lacosamide (3, 10, 30 or 50 mg/kg) or vehicle 10 minutes after the initiation of PPS to represent early treatment or 40 minutes after the initiation of PPS (ie, 10 minutes after the end of perorant pathway stimulation) to represent late treatment of SE.

2.4 Data recording, quantification of seizures and archiving

The telemetry transmitters had a high frequency cut off of 200 Hz and the computer-controlled system produced an analog output of ± 5 volts that was fed into the A/D board of a Stellate Systems (Montreal, CA) EEG monitor. Each channel of the Stellate system received data from a separate rat, with an average of four (maximum of eight) rats monitored concurrently. Harmony software (Stellate) was used to detect seizures, and digital video was recorded for 30 seconds before and after seizure detection. The seizure detection parameters were set somewhat low (amplitude criterion = 2, additional channel detections = 0, frequency criterion = 3, variability criterion = 70) to easily detect seizures in an effort to avoid false negatives. All types of electrographic seizure detection (types 1–4, reflecting factors such as high spike amplitude or frequency that increase the likelihood of the event being a seizure, 3–4 being a strong detection) were reviewed. Manual review of every seizure eliminated any false positives recorded. After one-half to three hours of seizure activity, some animals show “subtle” SE (Treiman et al 1990) with a burst suppression pattern on EEG, synchronous with mild myoclonic twitching. After 30 minutes or more of SE, these “subtle” behaviors were counted as seizures. Data were stored in Stellate file format on volumes of DVD under file names indicating the set of animals monitored and sub-numbered by sequential 12–24 hour periods continuing up to 16 days at the end of each counted seizure, and the date and time to the nearest 0.1 sec were recorded for the beginning and end of each seizure counted. Behavioral seizure severity was scored using the modified Racine scale (Haas et al., 1990) in which 0 = behavioral arrest; 1 = mouth clonus; 2 = head bobbing; 3 = head clonus; 4 = bilateral forelimb clonus; 5 = clonus with rearing and falling; 6 = wild running and jumping with vocalization; 7 = tonic seizure with hindlimb extension. As the behaviors displayed during stages 1 – 2 seizures (behavioral arrest, twitching of whiskers, wet dog shakes) are difficult to distinguish from normal rat behavior, behavioral seizure detections with less than stage 3 (forepaw clonus) were not counted.

2.5 Seizure monitoring

Acute SE—To investigate the effects of lacosamide for the treatment of acute status epilepticus induced by PPS, electrographic activity during the first 24 hours of SSSE was acquired continuously and analyzed off-line using Harmonie Software (Stellate Systems, Montreal, CA). The following indices were used to quantify seizure activity: the duration of SSSE (the time between the end of perorant path stimulation and the end of the last electrographic seizure); cumulative seizure time (duration of SSSE, subtracting interictal time); number of discrete seizure episodes; mean duration of individual seizures (cumulative seizure time divided by the number of seizures); number of spikes per hour.

Chronic Studies—To examine the occurrence of spontaneous recurrent seizures (SRS), animals were placed on EEG/telemetry/videotape for continuous EEG and video monitoring at least 6 weeks after SSSE induction (“latent period”). The following indices were quantified: total number of SRS over 7 days of observation, cumulative seizure time, number of spikes per week, the number of type-1/2 severity and type-3/4 severity seizures per week, light/dark distribution and the duration of individual seizures.

2.6 Statistical analysis

All statistical analyses were performed using Sigma Stat software (Ashburn, VA, USA). Data were analyzed using a one-way ANOVA followed by Newman-Keuls test, or if the normality test failed, an ANOVA on ranks (Kruskal-Wallis) test followed by Mann-Whitney *post hoc* test; $P < .05$ accepted as statistically significant. All results are presented as mean $\pm$ standard error of mean.

3. Results

3.1 Effects of early lacosamide treatment on acute status epilepticus

Intermittent PPS for 30 minutes induced SSSE in all 6 vehicle-treated rats (Figure 1), with a mean ($\pm$ SEM) number of seizures (combining electrographic and stage 3 or higher behavioral manifestations) of 185 ± 75 (median 77, geometric mean 123; 95% CI 45 to 338 seizures). Animals injected with 3 or 10 mg/kg of lacosamide showed no behavioral changes. At 30 mg/kg, there was mild motor incoordination for approximately half an hour, but they could still walk around the cage. After 50 mg/kg, spontaneous activity was reduced though the animals were conscious, able to walk and to right themselves when disturbed. Early treatment with lacosamide 10 minutes after the start of PPS ($n=6$ rats per dose group) resulted in a dose-dependent reduction in number of seizures (combining electrographic and stage 3 or higher behavioral manifestations), with significant effects ($P < .05$) noted with the administration of 10 mg/kg (69 ± 5 seizures), 30 mg/kg (12 ± 8 seizures), and 50 mg/kg lacosamide (19 ± 7 seizures; Figure 1A). Early lacosamide treatment also reduced cumulative seizure time in a dose-dependent manner, with significant decreases ($P < .05$) observed after treatment with 30 and 50 mg/kg lacosamide (3.7 ± 2.4 minutes after 30 mg/kg, and 5.8 ± 2.4 minutes after 50 mg/kg; Figure 1B) compared to vehicle-treated animals (54 ± 21 minutes).

Spike frequency did not change significantly compared to vehicle-treated rats (699 ± 91 spikes per hour) following the early administration of low doses of lacosamide (3 and 10 mg/kg), but showed significant reductions at the 30 and 50 mg/kg doses (311 ± 52 and 425 ± 47 , respectively). In all groups, a few late seizures and spikes persisted, and therefore no significant differences were seen in the duration of SE (time from end of stimulation to end of the last spontaneous seizure), the time of last spike, or the time needed to complete half of the seizures (half-life of SE). The mean duration of individual seizures, which is not usually altered by anticonvulsants, was similarly unchanged with early lacosamide treatment.

3.2 Effects of late lacosamide treatment on acute status epilepticus

Late treatment with lacosamide (40 minutes after the initiation of PPS) showed a trend toward a reduction in the number of seizures compared to vehicle-treated rats, but this trend was not significant. The mean (SEM) number of seizures was $185 (\pm 75)$ for vehicle-treated animals ($n=6$) as compared to $147 (\pm 32)$, $118 (\pm 39)$ and $113 (\pm 48)$ seizures following the administration of 10, 30 and 50 mg/kg lacosamide, respectively ($n=6$ for each dose; Figure 2A). Similarly, lacosamide showed a non-significant reduction in cumulative seizure time compared to control animals, with vehicle-treated rats having a mean cumulative seizure time of $54 (\pm 21)$ minutes compared to $42 (\pm 7)$, $34 (\pm 12)$ and $34 (\pm 15)$ minutes for animals treated with 10, 30 and 50 mg/kg lacosamide, respectively (Figure 2B). The frequency of spikes, duration of SE, time to last spike, time needed to complete half of the seizures, and the individual seizure durations did not statistically vary from control animals following late treatment with lacosamide.

3.3 Effects of early lacosamide administration on epileptogenic effects of SSSE

All 6 vehicle-treated rats in this study developed spontaneous recurrent seizures. Early lacosamide treatment dose-dependently reduced the number of SRSs from 110 (± 8) in vehicle-treated rats to 85 (± 5), 66 (± 8), 42 (± 8) and 34 (± 6) SRSs per week in rats treated with 3, 10, 30 or 50 mg/kg lacosamide ($n=3, 4, 5$ and 5), respectively (Figure 3A). The effects of the 30 and 50 mg/kg lacosamide doses were significantly different from vehicle treatment ($P<.05$). Early lacosamide treatment also resulted in a reduction of the cumulative SRS time, with 32 (± 3), 24 (± 3), 13 (± 1) and 12 (± 2) minutes /week of seizure time for rats treated with 3, 10, 30 or 50 mg/kg lacosamide, respectively, compared to 39 (± 4) minutes in vehicle-treated animals (Figure 3B); both the 30 and 50 mg/kg dose groups were significantly different from controls ($P<.05$). Similarly, spike frequency was reduced from 9534 ± 1114 spikes/week in vehicle-treated rats to 7557 (± 1945), 3536 (± 380), 2969 (± 542), and 2588 (± 370) spikes/week for the 3, 10, 30 and 50 mg/kg lacosamide-treatment groups, respectively (Figure 3C); these differences were significant for the 10, 30 and 50 mg/kg lacosamide groups ($P<.05$).

Examination of archived data for the occurrence of type-1/2 electrographic detections (recognized as weak detections by the Harmonie software) did not identify significant differences between vehicle-treated and lacosamide-treated rats; however, for stronger type 3/4 detections, a reduction in frequency of electrographic seizure detections was observed in high-dose lacosamide-treated animals compared to controls (Figure 3D). The weekly frequency of type-3/4 seizure detections was 72 (± 5) seizures per week in vehicle-treated rats compared to 36 (± 8), 40 (± 9), 24 (± 9) seizures per week with 3, 10, and 30 mg/kg lacosamide, respectively, but only 2 (± 1) seizures/week after lacosamide 50 mg/kg ($P<.05$). Although cumulative duration of seizure activity was significantly reduced compared to controls (Figure 3A), lacosamide-treatment, as expected, did not significantly reduce the mean duration of individual seizures.

3.4 Effects of late lacosamide administration on epileptogenic effects of SSSE

All 6 vehicle-treated animals showed SRSs as compared to 3 of 9 animals in the lacosamide 30 mg/kg and 50 mg/kg late treatment groups combined ($P<.05$). The pooled number of seizures/week in these two dose groups was 55 (± 32) compared to 110 (± 8) seizures per week for vehicle treated animals. The individual changes were 100 (± 7) in the 10 mg/kg lacosamide group, 67 (± 67) for 30 mg/kg lacosamide, and 45 (± 29) for 50 mg/kg lacosamide, none of which were significant; however, it should be noted that the median number of seizures in the 30 and 50 mg/kg lacosamide dose groups was 0, reflecting the fact that the majority of animals had no SRSs (Figure 4A). Late lacosamide treatment (30 and 50 mg/kg) showed a non-significant trend toward a reduction of the cumulative SRS time (Figure 4B), spike frequency (Figure 4C), the number of type 3/4 seizures (strong seizure detections by the software). As expected, mean duration of individual seizures was unaffected by treatment.

4. Discussion

The mechanisms whereby status epilepticus (SE) develops are not fully understood, though experimental models have provided molecular clues as to the nature of this serious neurological condition. The repeated, self-sustaining seizures that define SE alter the balance between excitatory and inhibitory pathways through maladaptive events that adversely affect or disrupt neurotransmitter and neuromodulator release, activation/deactivation of ion channels, receptor phosphorylation and desensitization, receptor trafficking and depletion, gene expression, neuronal health and energy reserves (Wasterlain and Chen, 2008). Such a broad range of physiologic and biochemical changes in the brain

therefore offers a multitude of potential targets for the effective treatment and management of SE. While current therapies work relatively well if given very early in the course of SE, they lose their efficacy quickly if seizures continue (Treiman et al., 1998). These clinical features can be reproduced experimentally using the perforant path stimulation model of SE, which is responsive to treatment with benzodiazepines or hydantoins (phenytoin and fosphenytoin) in the first 10 minutes of SE, but later becomes refractory to those agents (Mazarati et al., 1998). The results of this study show that lacosamide is an effective treatment for SE in the rat perforant path stimulation model, but loses potency when administered late in the course of SE. At doses of 10 mg/kg and above, early lacosamide administration reduced the number of seizures as well as the cumulative time spent seizing after treatment; higher lacosamide doses also reduced spike frequency. Other measures, such as mean duration of individual seizures and acute spiking duration, were not altered, but this was expected as typically those parameters do not respond to antiepileptic medications.

Previous experiments investigating the efficacy of lacosamide in preclinical rodent models of epilepsy have found that ED₅₀ doses ranged from 0.63 mg/kg in Frings mice to 9.99 mg/kg in the mouse 6-Hz model; in rats, the ED₅₀ in the MES test was 3.9 mg/kg and the effective dose for preventing amygdala kindling was 10 mg/kg (Brandt et al., 2006; Stöhr et al., 2007) indicating that the doses investigated in this study were similar to those that have demonstrated efficacy in other epilepsy models. Higher doses were not tested since we wanted to avoid significant drug-induced toxicity. The doses tested produced no or (at 50 mg/kg) only mild sedation, confirming the good CNS safety index of lacosamide compared with other AEDs (Beyreuther et al., 2007). The poor response to late treatment with lacosamide might limit its efficacy in clinical situations where treatment of SE is delayed. Diazepam also showed a rapid, time-dependent loss of potency with repeated seizures (Kapur and MacDonald, 1997; Mazarati et al 1998).

Lacosamide, an enhancer of sodium channel slow inactivation, differed in this respect from fosphenytoin, a pro-drug for an enhancer of sodium channel fast inactivation, which was still relatively effective at the 40-minute time point (but not at 70 minute) in this model (Mazarati et al 1998). However, this poor late response might be model-specific, since lacosamide was effective in the cobalt-homocysteine model of SE when injected 24.5 minutes after convulsant administration (Stohr et al 2007). It should also be noted that successful late administration of lacosamide in refractory human SE has been reported, as discussed below (Tilz et al 2010, Kellinghaus et al 2009)

The efficacy of lacosamide as an adjunctive treatment for refractory human partial-onset seizures has been demonstrated in 3 Phase II/III clinical trials (Ben-Menachem et al., 2007; Chung et al.; Halász et al., 2009). As replacement therapy, intravenous lacosamide administration is well tolerated (Biton et al., 2008; Doty et al., 2007), but human experience in SE is limited. Lacosamide was successfully used in a case involving a patient with nonconvulsive SE who had failed six previous AEDs (Kellinghaus et al., 2009). In that patient, intravenous lacosamide treatment (200 mg, followed by 200 mg/day orally) stopped rhythmic epileptiform activity within 3–5 minutes. A patient with convulsive SE refractory to diazepam, etomidate, midazolam, lorazepam and levetiracetam also responded to lacosamide administered through a gastric fistula (Tilz et al., 2010). However, of 7 patients treated with a 200 – 400 mg IV bolus of lacosamide for refractory SE, none had complications, but only 2 had a favorable response (Kellinghaus and Berning, 2009).

In this series of experiments using a preclinical model for SE, early treatment with lacosamide was more effective at reducing acute seizure activity than late treatment, which is similar to observations in animals and humans with other anticonvulsant drugs (Morrisett et al 1987, Suchomelova et al 2006). In the case of benzodiazepines, this seizure-induced

loss of potency may reflect seizure-induced receptor trafficking, resulting in a reduction of the number of GABA(A) receptors/synapse (Naylor et al., 2005); however, since lacosamide is believed to act mainly through the enhancement of sodium channel slow inactivation, the mechanism for the loss of antiseizure activity with delayed lacosamide treatment of SE is unclear.

The long-term effects of SSSE were attenuated by the early administration of lacosamide, with the number of SRSs being significantly reduced at the two highest doses tested. This might simply reflect a reduction of the number and cumulative duration of acute seizures (Figure 1). Late treatment with lacosamide did not significantly reduce duration or severity of acute SE, but produced a significant decrease in chronic SRSs when results from the two high-dose groups were pooled. The majority of animals from the highest two dose groups (30 and 50 mg/kg) were seizure-free ($P < .05$ compared to controls, none of which were seizure-free), and severe seizures (type-3/4) were reduced. More studies are needed to determine the significance of these effects of lacosamide on SE-induced epileptogenesis.

To summarize, in this model of SE, lacosamide treatment was effective in limiting the number of seizures and in reducing their long-term consequences when administered early. The results of this series of animal experiments suggest that lacosamide should be further investigated as a potential treatment for status epilepticus.

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Figure 1.

Acute effects of early treatment of SSSE with lacosamide. * indicates $P < .05$ and error bars indicate $\pm$ SEM. (A) Effect of early treatment on number of seizures. (B) Effect of early treatment on cumulative seizure time.

Figure 2. Acute effects of late treatment of SSSE with lacosamide. Error bars indicate $\pm$ SEM. (A) Effect of late treatment on number of seizures. (B) Effect of late treatment on cumulative seizure time.

Figure 3.

Long-term effects of early treatment of SSSE with lacosamide. * indicates $P < .05$ and error bars indicate $\pm$ SEM. (A) Effect of early treatment on number of spontaneous recurrent seizures/week. (B) Effect of early treatment on cumulative duration of spontaneous recurrent seizures. (C) Effect of early treatment on number of spikes/week. (D) Effect of early treatment on the number of electrographic type-3/4 spontaneous recurrent seizure detections/week.

Figure 4.

Long-term effects of late treatment (40 minutes after initiation of perforant path stimulation) with lacosamide. * indicates $P < .05$ and error bars indicate $\pm$ SEM. (A) Effect of late treatment on number of spontaneous recurrent seizures/week. (B) Effect of late treatment on cumulative duration of spontaneous recurrent seizures. (C) Effect of late treatment on number spikes/week. (D) Effect of late treatment on the number of type-3/4 spontaneous recurrent seizures/week.