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Effect of perampanel, a novel AMPA antagonist, on benzodiazepine-resistant status epilepticus in a lithium-pilocarpine rat model

Takahisa Hanada[1,2], Katsutoshi Ido[1] & Takashi Kosasa[1]

[1]Global Biopharmacology, Neuroscience & General Medicine Product Creation System, Eisai Co., Ltd, Tsukuba, Ibaraki, Japan
[2]Center for Tsukuba Advanced Research Alliance, Graduate School of Life and Environmental Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan

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Correspondence
Takahisa Hanada, Eisai Co., Ltd, 5-1-3 Tokodai, Tsukuba, Ibaraki 300-2635, Japan. Tel: +81 29 847 6944. Fax: +81 29 847 5738. E-mail: t-hanada@hhc.eisai.co.jp

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Abstract

This study assessed the efficacy of diazepam, and the alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor antagonists perampanel and GYKI52466 in a lithium-pilocarpine status epilepticus (SE) model. SE was induced in rats using lithium chloride, scopolamine methyl bromide, and pilocarpine. Diazepam 10, 20, or 40 mg kg^{-1}, or perampanel 1, 2.5, 5, or 8 mg kg^{-1} were administered intravenously at 10 or 30 min after seizure onset, and GYKI52466 50 mg kg^{-1}, or combinations of diazepam 2.5–5 mg kg^{-1} and perampanel 0.5–1 mg kg^{-1}, were administered intravenously at 30 min after seizure onset. Diazepam 20 mg kg^{-1} terminated seizures (based on electroencephalography and assessment of behavioral seizures) in 2/6 rats at 10 min and 0/6 rats at 30 min (ED_{50}: 10 min, 30 mg kg^{-1}; 30 min, not determined). Perampanel 8 mg kg^{-1} terminated seizures in 6/6 rats at both 10 and 30 min (ED_{50}: 10 min 1.7 mg kg^{-1}; 30 min, 5.1 mg kg^{-1}). GYKI52466 50 mg kg^{-1} terminated seizures in 2/4 rats at 30 min. Co-administration of diazepam 5 mg kg^{-1} and perampanel 1 mg kg^{-1} terminated seizures in 9/9 rats at 30 min. In conclusion, perampanel and GYKI52466 provided efficacy in a lithium-pilocarpine SE model at 30 min after seizure onset, when SE was refractory to diazepam, supporting the therapeutic potential of AMPA receptor antagonists for refractory SE. The perampanel dose required to terminate seizures was reduced by combination with diazepam, suggesting synergy.

Abbreviations

AED, antiepileptic drug; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; CI, confidence interval; CNS, central nervous system; ED_{50}, dose required to terminate seizures in 50% of animals; EEG, electroencephalography; GABA, γ-amino butyric acid; RSE, refractory status epilepticus; SE, status epilepticus.

Introduction

Status epilepticus (SE) is a prolonged, self-sustained seizure that is associated with substantial mortality and morbidity (Hui et al. 2003; Shneker and Fountain 2003; Chin et al. 2004). Although a consistent definition is yet to be agreed, recent guidelines have proposed that SE is characterized by ≥5 min of (a) continuous clinical and/or electrographic seizure activity, or (b) recurrent seizure activity without recovery between seizures (Brophy et al. 2012).

It is recommended that SE is treated rapidly with benzodiazepines (e.g., diazepam) followed by intravenously administered antiepileptic drugs (AEDs; e.g., phenytoin) (Meierkord et al. 2006, 2010; Brophy et al. 2012). However, SE is often refractory to treatment, increasing the risk of poor outcomes (Rossetti et al. 2005; Novy et al. 2010; Hocker et al. 2013; Sutter et al. 2013). In a study of

adults with SE, 22.6% of cases did not respond to first- or second-line treatment, and these cases were associated with higher mortality rates than non-refractory SE (39% vs. 11%) (Novy et al. 2010). Refractory SE (RSE) can necessitate referral to an intensive care unit and treatment with anesthetizing AEDs, such as midazolam, propofol, or barbiturates, to help prevent severe acute systemic and long-term neuronal consequences (Meierkord et al. 2006, 2010; Brophy et al. 2012).

SE is thought to be a consequence of dysfunction in the neuronal machinery required for the termination of seizures: specifically, a loss of inhibitory γ-amino butyric acid (GABA) neuronal activity coupled to sustained glutamate-mediated excitatory activity (Naylor et al. 2005; Chen and Wasterlain 2006; Naylor 2010; Deeb et al. 2012). In the lithium-pilocarpine rat model of SE there is a functional loss of postsynaptic $GABA_A$ receptors ~1 h after seizure onset and this is associated with internalization of the receptor to the cytoplasm (Naylor et al. 2005). Loss of GABA-mediated inhibitory activity may also be a result of changes in chloride homeostasis, as the inhibitory effects of $GABA_A$ receptors are mediated by chloride flux (Chen and Wasterlain 2006; Deeb et al. 2012). Anesthetizing AEDs that enhance GABA activity are currently used to treat RSE (Meierkord et al. 2006, 2010), but novel approaches targeting non-GABAergic mechanisms may help to improve treatment outcomes.

Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors mediate excitatory glutamate neurotransmission in the central nervous system (CNS) and play an important role in seizure initiation and propagation of seizure activity (Rogawski 2011). In a study of AMPA receptor-mediated neurotransmission in a lithium-pilocarpine rat model of SE, RSE was associated with a selective reduction in surface expression of the GluA2 subunit of the AMPA receptor on hippocampal membranes and an increase in GluA2 subunit internalization rates (Rajasekaran et al. 2012). This resulted in calcium-permeable GluA2-lacking AMPA receptors with distinct biophysical characteristics, and continued neurotransmission. This synaptic plasticity may be an important pathophysiologic change in SE leading to subsequent neurodegeneration and increased mortality and morbidity. Therefore, inhibition of AMPA receptor activity may have potential as a therapeutic approach for the treatment of RSE.

The therapeutic potential of AMPA receptor inhibition has been supported by animal studies in which AMPA receptor antagonists, such as GYKI52466, have been shown to terminate seizures in models of benzodiazepine-resistant SE (Pitkanen et al. 2007; Fritsch et al. 2010; Langer et al. 2011; Rajasekaran et al. 2012). Another AMPA receptor antagonist that may confer benefit in this setting is perampanel, which has been approved by the European Medicines Agency and the US Food and Drug Administration as an adjunctive treatment for partial-onset seizures, with or without secondary generalization, in patients aged ≥12 years (European Medicines Agency 2012; Food and Drug Administration 2012). Perampanel demonstrated broad-spectrum anti-seizure activity when given orally in preclinical animal models, including models of tonic-clonic generalized seizures, absence/myoclonic seizures, and temporal lobe epilepsy (Hanada et al. 2011). In this study, we assessed the efficacy of diazepam, and the AMPA receptor antagonists perampanel and GYKI52466, in the lithium-pilocarpine rat model of SE. Overall, we demonstrate that perampanel and GYKI52466 can provide efficacy in this model at 30 min after seizure onset, when the SE is refractory to diazepam, supporting the therapeutic potential of AMPA receptor antagonists for RSE.

Materials and Methods

Animals

Male Sprague Dawley rats (Charles River Laboratories, Kanagawa, Japan) weighing 240–400 g were housed in cages in a controlled environment (constant temperature 22 ± 1°C; humidity 50–60%; 12-h dark/light cycle [lights on 07:00–19:00 h]) with free access to food (MF diet; Oriental Yeast Co., Tokyo, Japan) and water. All experiments were approved by the Committee for the Welfare of Laboratory Animals of Eisai Co., Ltd.

Materials

Lithium chloride (Wako Pure Chemical Industries, Osaka, Japan), pilocarpine (Wako Pure Chemical Industries), and scopolamine methyl bromide (Sigma-Aldrich, Tokyo, Japan) were dissolved in 0.9% sodium chloride solution. Diazepam (Wako Pure Chemical Industries), perampanel (Eisai Co., Ltd, Kashima, Japan), and GYKI52466 (Sigma-RBI, St Louis, MO) were prepared in 1:1:1 (v/v) distilled water, dimethyl sulfoxide, and polyethylene glycol 300.

Surgical procedures for implantation of electrodes

Rats were acclimatized for at least 1 week prior to surgery. On the day of surgery, rats were anesthetized with pentobarbital 50 mg kg^{-1} (somnopentyl injection; Kyoritsu Seiyaku, Tokyo, Japan) administered intraperitoneally (i.p.) and surface electroencephalography (EEG) electrodes (XR2C-2011-N; Omron, Kyoto, Japan) were positioned epidurally in the skull using stereotaxic

surgery. One electrode was placed over the right somatosensory cortex (2.5 mm posterior from the bregma and 3.0 mm lateral to the midline) according to the coordinates of Paxinos and Watson (2007), with another reference electrode placed over the right cerebellum. Electrodes were fixed to the skull with acrylic dental cement. After electrode implantation, rats were returned to their home cage and allowed to recover.

Induction of status epilepticus

At least 1 week after implantation of EEG electrodes, and 16–24 h before pilocarpine treatment, rats were treated with lithium chloride 3 mEq kg^{-1} i.p. On the day of testing, rats were placed in acrylic boxes and baseline EEG was recorded (Lab Charts® 7 v7.2; AD Instruments, Sydney, Australia) for at least 10 min. Rats were then injected with scopolamine methyl bromide 5 mg kg^{-1} i.p. and pilocarpine 30 mg kg^{-1} i.p. The dose and timing of scopolamine methyl bromide injection was selected to confer inhibition of the peripheral side effects of pilocarpine (salivation, diarrhea, lacrimation), which was not achieved with the standard regimen of scopolamine methyl bromide 1 mg kg^{-1}, administered 30 min prior to pilocarpine. In addition, the selected regimen of scolpolamine methyl bromide appeared to reduce the potential for respiratory problems, which occasionally resulted in animal death, apparently due to the aspiration of saliva, when the standard regimen of scopolamine methyl bromide was used prior to the administration of high doses of perampanel or diazepam. The higher dose used here slowed seizure onset, but did not change the subsequent course of SE. Seizure onset was designated as the first spike train in EEG recording (not as the start of SE).

Drug treatment

Diazepam, perampanel, and GYKI52466 were administered by bolus intravenous (i.v.) injection to the rat tail vein after seizure onset.

Diazepam has previously been shown to terminate or attenuate kainic acid-induced SE in rodents when administered 5 min to 2 h after seizure onset at doses of 20–25 mg kg^{-1} i.p. (Pitkanen et al. 2007; Fritsch et al. 2010); therefore a dose range of 10–40 mg kg^{-1} i.v. was selected for this study. Diazepam doses of 10, 20, or 40 mg kg^{-1} i.v. were administered to groups of six rats at 10 min after seizure onset. Doses of 20 or 40 mg kg^{-1} i.v. were also administered to six or seven rats, respectively, at 30 min after seizure onset.

In pilot experiments using the lithium-pilocarpine rat model of SE, perampanel 8 mg kg^{-1} consistently terminated seizures and was well tolerated; therefore, a maximum dose of 8 mg kg^{-1} i.v. was selected for this study. Perampanel 1, 2.5, 5, or 8 mg kg^{-1} i.v. was administered at 10 min after seizure onset to groups of six rats each. Perampanel doses of 2.5, 5 or 8 mg kg^{-1} i.v. were also administered at 30 min after seizure onset, all to groups of six rats.

A GYKI52466 dose of 50 mg kg^{-1} was selected based on the effective dose in kainic acid-induced SE in mice (Fritsch et al. 2010). GYKI52466 50 mg kg^{-1} i.v. was administered at 30 min after seizure onset to four rats.

Diazepam 2.5 or 5 mg kg^{-1} and perampanel 0.5 or 1 mg kg^{-1} were administered alone or in combination at 30 min after seizure onset. These doses were based on preliminary studies in which diazepam 5 mg kg^{-1} i.v. in combination with perampanel 2 mg kg^{-1} i.v. was shown to terminate seizures in two rats when administered at 30 min after seizure onset (T. Hanada, unpubl. data).

Assessment of seizure termination

Seizures were considered terminated if EEG spike activity was abolished, EEGs were spike-free at 30 min after drug dosing, and there was a lack of behavioral seizures. Behavioral seizures were classified according to Racine (1972): stage 1 – immobility, eye closure, twitching of vibrissae, sniffing, facial clonus; stage 2 – head nodding associated with more severe facial clonus; stage 3 – clonus of one forelimb; stage 4 – rearing, often accompanied by bilateral forelimb clonus; stage 5 – all of the above plus loss of balance and falling, accompanied by generalized clonic seizures.

Statistical analyses

Doses required to terminate seizures in 50% of animals (ED_{50} values) were calculated by computer probit analysis using SAS version 9.3 (SAS Institute, Tokyo, Japan). Clear separation of 95% confidence intervals (CIs) was used to confirm a statistically significant difference in ED_{50} values when doses were administered at 10 or 30 min after seizure onset.

Results

Lithium-pilocarpine-induced status epilepticus

Approximately 15–30 min after pilocarpine administration, rats exhibited a train of spikes in EEG recordings that grew progressively larger (seizure onset; Fig. 1). Continuous EEG spikes and behavioral generalized seizures developed within 10 min of seizure onset, indicating establishment of SE, and were maintained for at least

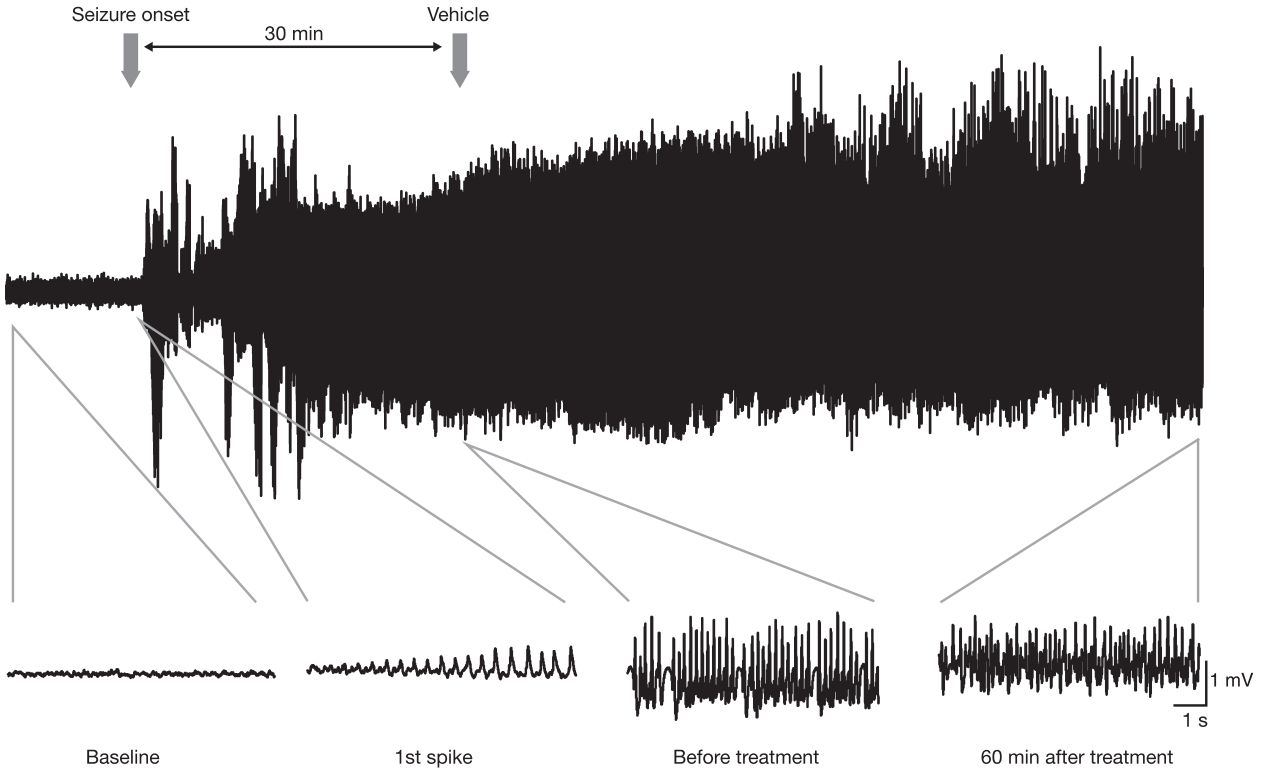

Figure 1. Representative status epilepticus electroencephalogram induced by lithium pilocarpine in rats.

180 min. Administration of vehicle (i.v.) did not affect the continuous EEG spikes.

Effect of drug treatment on seizure termination

Diazepam

When administered 10 min after seizure onset, diazepam terminated seizures at an ED_{50} of 30 mg kg^{-1} (95% CI, 17–130 mg kg^{-1}; Table 1). A dose of 20 mg kg^{-1} i.v. terminated EEG seizures in two of six rats when administered at 10 min (Fig. 2), and also conferred strong muscle relaxation, such that no visible behavioral seizures persisted. However, when administered 30 min after seizure onset, diazepam 20 mg kg^{-1} i.v. failed to terminate EEG seizures, and a higher dose of 40 mg kg^{-1} was only effective in one of seven rats (Table 1; Fig. 2).

Perampanel

Perampanel terminated seizures at an ED_{50} of 1.7 mg kg^{-1} (95% CI 0.3–3.8 mg kg^{-1}) when administered 10 min after seizure onset, and 5.1 mg kg^{-1} (95% CI 4.9–5.2 mg kg^{-1}) when administered at 30 min (lack of overlap of 95% CI values indicates a significant reduction in efficacy between 10 and 30 min; Table 1). In contrast to diazepam, perampanel 8 mg kg^{-1} i.v. immediately terminated seizures in six of six rats whether administered at 10 or 30 min (Fig. 2).

Table 1. Dose-dependent effects of diazepam and perampanel on lithium-pilocarpine-induced seizures in rats.

	10 min after seizure onset	30 min after seizure onset
Diazepam		
Rats in which seizures were terminated (*n*/*N*)		
10 mg kg^{-1} i.v.	0/6	NR
20 mg kg^{-1} i.v.	2/6	0/6
40 mg kg^{-1} i.v.	4/6	1/7
ED_{50}, mg kg^{-1} (95% CI)	30 (17–130)	ND
Perampanel		
Rats in which seizures were terminated (*n*/*N*)		
1 mg kg^{-1} i.v.	1/6	NR
2.5 mg kg^{-1} i.v.	5/6	0/6
5 mg kg^{-1} i.v.	5/6	2/6
8 mg kg^{-1} i.v.	6/6	6/6
ED_{50}, mg kg^{-1} (95% CI)	1.7 (0.3–3.8)	5.1 (4.9–5.2)

CI, confidence interval; ED_{50}, dose required to terminate seizures in 50% of animals; i.v., intravenous; ND, not determined; NR, not reported.

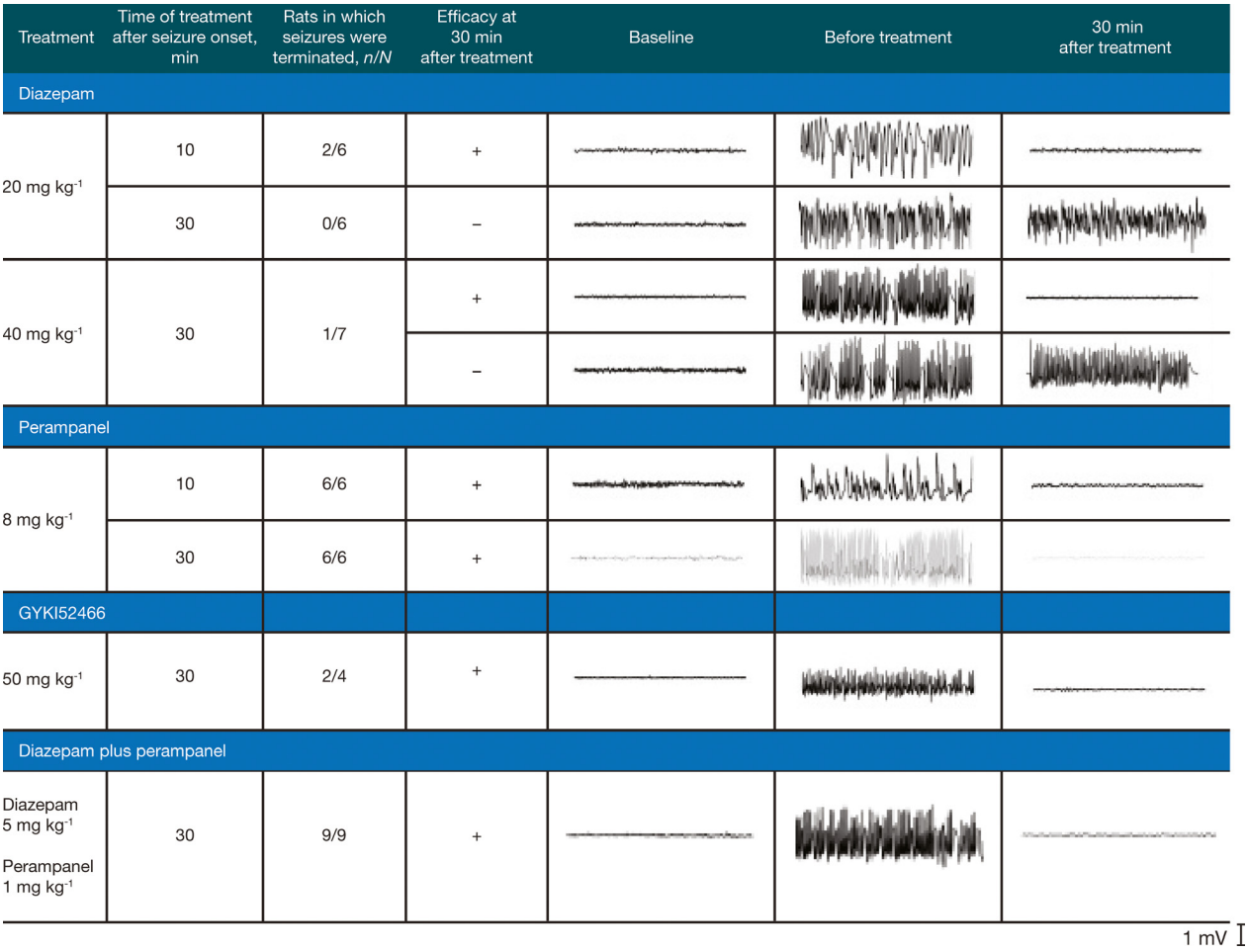

Figure 2. The effect of diazepam, perampanel or GYKI52466 on lithium-pilocarpine-induced status epilepticus electroencephalogram (EEG); each EEG trace spans 10 sec.

GYKI52466

Consistent with the results observed with perampanel, GYKI52466 50 mg kg^{-1} i.v. terminated seizures in 2 of 4 rats when administered 30 min after seizure onset (Fig. 2): there was a gradual reduction of seizure activity in one rat, with seizure termination within 30 min, and an immediate termination of seizures in the second animal.

Diazepam and perampanel

Diazepam 20 mg kg^{-1}, perampanel 8 mg kg^{-1}, and GYKI52466 50 mg kg^{-1} caused strong CNS depressant effects (immobility, loss of righting reflex) during observation in all rats, with higher doses of diazepam and perampanel compromising respiration in some cases. Therefore, in an attempt to reduce CNS inhibition, the combination of lower doses was explored.

When diazepam 5 mg kg^{-1} i.v. was administered in combination with perampanel 1 mg kg^{-1} i.v. at 30 min after seizure onset, seizures were terminated in all rats (n = 9; Fig. 2). At lower doses, seizures were terminated in two of four rats (diazepam 2.5 mg kg^{-1}, perampanel 1 mg kg^{-1}) and two of six rats (diazepam 5 mg kg^{-1}, perampanel 0.5 mg kg^{-1}) (Fig. 3).

The combination of low doses of diazepam and perampanel was still associated with strong CNS depressant effects, but recovery of righting reflex was observed sooner than with higher-dose monotherapy.

Mortality

No deaths occurred during the observation periods of any of the studies reported here, irrespective of treatment.

Discussion and Conclusions

In this lithium-pilocarpine rat model, continuous EEG spikes, indicative of the development of SE, were observed

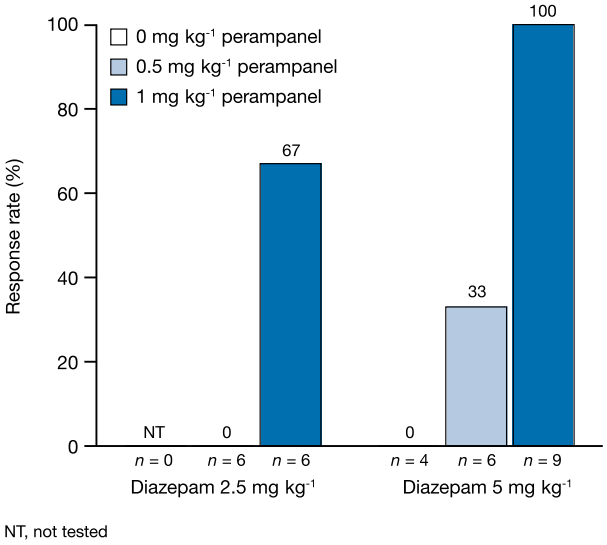

Figure 3. Effect of combined treatment with perampanel and diazepam on lithium-pilocarpine-induced seizures when administered intravenously 30 min after seizure onset.

within 10 min of seizure onset. Diazepam i.v. terminated seizures at an ED_{50} of 30 mg kg^{-1} when administered 10 min after seizure onset. However, when administered at 30 min after seizure onset, no animals responded to diazepam 20 mg kg^{-1}, and only one of seven animals responded to diazepam 40 mg kg^{-1}, suggesting that refractoriness to benzodiazepine had started to develop by this time point. It is well recognized that pharmacoresistance to benzodiazepines develops rapidly in the lithium-pilocarpine rat model, and the current results appear to be in accordance with this. For example, diazepam 20 mg kg^{-1} was able to stop SE in the lithium-pilocarpine rat model when administered at the early stage of discrete electrographic seizures, but became less effective when administered at later stages of SE (Walton and Treiman, 1988). Similarly, it has been reported that diazepam i.p., at doses of up to 20 mg kg^{-1}, provided some efficacy at 10 min after the development of a stage 3 seizure in the lithium-pilocarpine rat model, but not at later time points (Jones et al. 2002).

In contrast, perampanel i.v. terminated seizures at an ED_{50} of 1.7 mg kg^{-1} when administered 10 min after seizure onset, and continued to provide efficacy at 30 min with an ED_{50} of 5.1 mg kg^{-1}. A dose of perampanel 8 mg kg^{-1} terminated seizures in all animals at 30 min after seizure onset, and, similarly, GYKI52466 50 mg kg^{-1} was also able to terminate seizures in some animals at this time point. These data are in accordance with previous studies of AMPA receptor antagonists in animal models of SE (Pitkanen et al. 2007; Fritsch et al. 2010; Langer et al. 2011; Rajasekaran et al. 2012) and support the potential efficacy of agents with this mechanism of action in benzodiazepine-RSE.

Previous research using animals models of SE has indicated that repeated i.p. injections of GYKI52466 are required to terminate seizures (Fritsch et al. 2010), but a single i.v. injection was sufficient to cease seizures in this study. This discrepancy may reflect the different administration routes, since i.v. administration may be expected to increase plasma concentrations more rapidly, and to a greater extent, than i.p. administration.

SE has been associated with internalization of $GABA_A$ receptors to the cytoplasm at just 1 h after seizure onset (Naylor et al. 2005). In accordance with this, evidence from animal models also suggests that plastic changes in $GABA_A$ receptor function occur rapidly during the development of SE (Feng et al. 2008). Such functional changes have previously been associated with decreases in the sensitivity of SE to benzodiazepines over time in the lithium-pilocarpine rat model (Walton and Treiman 1988; Kapur and Macdonald 1997; Feng et al. 2008), as was observed with diazepam at the 30-min time point in the present study. In contrast, while expression of the AMPA receptor subunit GluA2 has been found to be reduced in SE, similar receptor function may be provided by GluA2-lacking AMPA receptors (Rajasekaran et al. 2012). This is consistent with our findings that AMPA receptor antagonists continue to provide efficacy for the treatment of SE at 30 min.

However, the efficacy of perampanel appeared to wane over time, as the ED_{50} value for the termination of seizures was greater when perampanel was administered 30 min after seizure onset than when it was administered at 10 min. Given these timings, and the potential interactions of the GABA and AMPA systems indicated by the synergistic effects of co-administering perampanel and diazepam, such a decline in efficacy may be associated with the early changes in $GABA_A$ receptor function.

Diazepam 20 mg kg^{-1}, perampanel 8 mg kg^{-1}, and GYKI52466 50 mg kg^{-1} caused strong CNS depressant effects (immobility, loss of righting reflex) in all rats. Although such effects may be justified by the termination of SE, it is important to explore approaches to improve tolerability while maintaining efficacy. High doses of AEDs have been associated with substantial toxicity in animal models (Morimoto et al. 1997), and we, therefore, hypothesized that administration of lower doses of perampanel might be useful in optimizing safety outcomes. Combination therapy was explored as an option to reduce dosing because synergistic effects have previously been reported with AEDs in the lithium-pilocarpine model, including diazepam in combination with *N*-methyl-D-aspartate receptor antagonists (Rice and DeLorenzo 1999;

Martin and Kapur 2008). We report that seizures were consistently terminated in the lithium-pilocarpine rat model by the co-administration of low doses of diazepam (5 mg kg^{-1}) and perampanel (1 mg kg^{-1}) at 30 min after seizure onset, similar to the efficacy observed at this time point with perampanel 8 mg kg^{-1} alone. Although CNS depressant effects were observed with both approaches, recovery of righting reflex occurred more quickly with the low-dose combination therapy. These results indicate synergistic effects that may reduce the required therapeutic dose of perampanel in the presence of diazepam, conferring improved safety outcomes. Similarly, a subclinical dose of the AMPA antagonist LY-300164 has been shown to significantly inhibit seizures in amygdala-kindled seizure models when combined with low-dose benzodiazepines, but the combination did not cause the motor impairment or memory deficits observed with higher-dose benzodiazepine monotherapy (Borowicz et al. 1999, 2000).

Previously, oral perampanel has been found to reduce the incidence of 6-Hz electroshock-induced seizures in mice at doses of 1–8 mg kg^{-1}, with lower doses required to achieve similar efficacy when co-administered with carbamazepine, phenytoin, or valproate (Hanada et al. 2011). However, in our lithium-pilocarpine SE model, there were no such interactions between perampanel 2 mg kg^{-1} and phenytoin 50 mg kg^{-1} ($n = 4$), and only a weak interaction between perampanel 2 mg kg^{-1} and valproate 300 mg kg^{-1} (seizures terminated in 2/6 rats; data not shown). Therefore, synergistic effects may depend on the seizure type and condition, and the interactions between perampanel and diazepam observed in the present study may be specific to benzodiazepine-resistant SE.

As yet, there are no established therapies for RSE that directly attenuate neuronal excitation through the inhibition of glutamate receptors, with current guidelines recommending the use of anesthetizing AEDs that enhance GABA activity (Meierkord et al. 2006, 2010). However, studies using the lithium-pilocarpine rat model support the further investigation of AMPA receptor antagonists in RSE.

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Disclosures

T. Hanada, K. Ido, and T. Kosasa are employees of Eisai Co., Ltd.

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