Talampanel

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Summary: Talampanel is a novel anticonvulsant that acts as an allosteric inhibitor of the AMPA receptor. Talampanel has a broad spectrum of action in animal models of epilepsy and neuroprotection. Clinical experience to date has been able to show effectiveness in reduction of seizures in patients with refractory partial seizures. **Key Words:** AMPA, epilepsy, glutamate, neuroprotection, talampanel

INTRODUCTION

Glutamate is the principal excitatory neurotransmitter in the mammalian CNS and has been implicated in numerous neurological diseases, including epilepsy. In pathological conditions in which excess glutamate is released, the excitotoxic cascade leads to excessive cytoplasmic calcium, resulting in apoptosis and neuronal death. A role for glutamate in epilepsy is suggested by a number of observations. In animal studies, excess glutamate has been observed during seizures and is attenuated by actions of transporter proteins.[1] Glutamate receptor agonists will induce seizures, and there is an increased occurrence of seizures in transgenic rats in which there is a decreased expression of glutamate transporters.[2] Glutamate acts at numerous receptor sites in the CNS, including NMDA (*N*-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid), and kainite. The role of AMPA receptors in epilepsy has been extensively reviewed by Rogawski and Donevan.[3]

Talampanel (TLP) was developed as a noncompetitive (allosteric) antagonist of the AMPA receptor from a series of novel 2,3-benzodiazepines. These molecules, though similar in structure to the conventional 1,4-benzodiazepines, do not share the same pharmacology and do not interact at the benzodiazepine–GABA receptor complex.

Talampanel is active in various animal models of epilepsy, which will be described here. It is active in the prevention of kindling, an action thought to be related to epileptogenesis. It is also active in various animal models of neuroprotection.

The actions of TLP at the AMPA receptor were described by Lodge et al.[4] In this work, NMDA, AMPA, and kainite were respectively administered *in vivo* to spinal neurons in anesthetized rats, and the results were examined. In the presence of TLP, but not its (+) isomer, the response to AMPA was inhibited, demonstrating a selective and stereoselective action of TLP for the AMPA receptor. Talampanel does not act directly on the AMPA receptor, but at an allosteric site referred to as the GYKI receptor.[5]

The objective of this review is to summarize the elements of the preclinical pharmacology of TLP that support its development as a novel therapy for epilepsy, as well as to review the information available from clinical studies.

PHARMACOLOGY

Anticonvulsant activity in animals

Talampanel has a broad spectrum of activity in animal models of epilepsy.[6] These data are summarized in Table 1.

The maximum electroshock (MES) model is generally considered to be the model most predictive of activity in humans, and at the ED_{50} dose in mice, TLP caused very little CNS impairment.[6] In another series of experiments performed by a group in Lublin, Poland, it was shown that AMPA antagonists potentiated the protective actions of other anticonvulsants in animal models. This was initially demonstrated with GYKI 52466, a close analog of TLP.[7] In later experiments, this group demonstrated

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TABLE 1. *Anticonvulsant Activity of Talampanel in Mice*

Seizure Model	ED_{50}, mg/kg p.o.
Maximal electroshock	8.6
Metrazole	16.8
Strychnine	17.4
Bemegride	23.9
Bicuculline	14.6
Nicotine	22.7
4-AP	8.4
3-MPA	17.1

Source: Szelenyi et al.[6]
Talampanel was administered orally as a suspension 1 h before the seizure stimulus.
3-MPA = 3-mercaptopropionic acid; 4-AP = 4-aminopyridine.

that subprotective doses of TLP (2 mg/kg p.o.) potentiated the anticonvulsant effect of diazepam in mice, using the MES and metrazole models of epilepsy.[8] Furthermore, TLP at subprotective doses (0.3125–1.25 mg/kg p.o.) protected against amygdala-kindled seizures in rats.[8] The observation that TLP is active in kindled rats is of great interest, in that this model is thought to be able to distinguish between the antiseizure activity of a drug and its potential antiepileptogenic effects. Talampanel is also effective in animal models of neuroprotection, as described in the next section.

Subprotective doses of TLP enhanced the protective effects of valproate, diphenylhydantoin, and phenobarbital in the mouse MES procedure.[9] Similar findings were reported with valproate, carbamazepine, and diazepam for aminophylline-induced convulsions in mice.[10]

A rat model that is used to predict activity in absence epilepsy uses WAG/Rij strain of rats and evaluates the ability of a compound to generate spike wave discharges in parallel to vigilance and behavioral changes.[11] Early studies had reported that the TLP analog GYKI 52466 was effective in this procedure, but studies with the racemate of TLP (GYKI 53405) failed to show any effects at doses of 16 mg/kg i.p.[11]

Neuroprotective effects of TLP in animals

The neuroprotective effects of TLP have been evaluated in a variety of models. In the gerbil bilateral carotid artery occlusion model, TLP provided survival of up to 25% of hippocampal CA1 neurons, although the (+) isomer of TLP did not.[4] Talampanel is neuroprotective in other rodent stroke models.[12] The results of these studies are summarized in Table 2.

In a later study by the same authors,[13] the sensory motor function was monitored for 30 days in rats after a 60-min middle cerebral artery occlusion (MCAO). Talampanel at a dose of 10 mg/kg i.p. was given six times at 30-min intervals starting 30 min after the MCAO. Animals were compared to controls and sham-operated animals. The general well-being, neurological status, spontaneous motor activity, rotation, motor coordination, balancing, muscle strength, and reaction time were followed for 1 month. Talampanel improved coordination in rotarod ($p < 0.01$) and beam walking ($p < 0.01$) and reduced the number of MCAO-induced rotations ($p < 0.05$).

GYKI 53405, the racemate of TLP administered by intraperitoneal injection, prolonged the survival time in mice receiving an intravenous dose of MgCl.[14]

In addition to the stroke models described earlier, TLP has been evaluated in a model of traumatic brain injury in rats.[15]

TABLE 2. *Acute Effect of Talampanel on Rodent Models of Focal Cerebral Ischemia*

Species (Strain)	Induction of Lesion[22-24]	Duration of Insult	Dose Regimen	Time to 1st Dose After Insult	Reduction in Lesion vs. Vehicle Control, %	*p*
Rat (SD)	Focal ischemia by ligation of middle cerebral artery	60 min	6 × 2 mg/kg i.v. every 30 min	30 min	47.3	<0.01
		60 min	Same	2 h	48.5	<0.01
		60 min	Same	3 h	24.0	>0.05
Mouse (C57BL/6J)	Focal ischemia by ligation of internal carotid artery	90 min	6 × 2 mg/kg i.p. every 15 min	15 min	44.5*; 39.3†	<0.05*; <0.01†
		2 h	Same	15 min	37.0*; 37.0†	<0.05*; <0.05†
		24 h	Same	15 min	No protection	
Rat (CD)	Photothrombosis	20 min	6 × 2 mg/kg i.v., or 6 × 4 mg/kg i.v., or 6 × 6 mg/kg i.v.	30 min	40.1‡	<0.05‡

*Striatum. †Hippocampus. ‡Composite result of all three doses.

The injury was produced by fluid percussion and a pressure transient of 1.5–2.0 atm was delivered to the right dorsolateral parietal cortex. Treatment with TLP, as a 4 mg/kg bolus followed by 4 (mg/kg)/h over 72 h, was administered intravenously beginning at either 30 min or 3 h after trauma or sham surgery. Talampanel, starting at the 30-min time, attenuated neuronal damage in three sectors of the hippocampal CA1 sector compared to placebo. If started 3 h after the injury, however, TLP was ineffective.

Studies in human volunteers

Talampanel is generally well tolerated in human volunteers. Dizziness has been the most commonly reported adverse event, with some sedation and ataxia reported at higher doses.[16]

In humans, TLP is well absorbed. The mean time to reach peak concentration (T_{max}) is approximately 2 h, with an elimination half-life $T_{1/2}$ in healthy volunteers of approximately 4 h, and approximately 3 h in subjects on enzyme inducers. Part of the TLP is converted to N-acetyl-TLP by hepatic N-acetyl transferase 2 (NAT-2). Phenotypically, there are at least three types of subjects with respect to NAT-2. Subjects are either fast, slow, or intermediate acetylators and thus have been converted with distinct genotypes. The impact of this phenotype on the kinetics of TLP was studied in both fasted and fed subjects.[17]

The results of this study suggest that, although N-acetylation represents only a relatively small fraction of the elimination, and plasma TLP values are unaffected by NAT-2 phenotype, there were significant differences in the plasma levels of N-acetyl TLP, which is an active molecule and could be a factor in the profile of adverse effects observed in patients. The main effect of a high-fat or high-calorie meal on TLP pharmacokinetics was a delay in T_{max} (from 1.90 h to 2.41 h), but no other major differences in the kinetic parameters. Based on these data and data from another study in which subjects were phenotyped, a pharmacokinetics model was developed that can predict plasma levels of TLP and N-acetyl TLP in the three main phenotypes of NAT-2.[18]

An interaction study with valproic acid[19] (VPA) was conducted in healthy volunteers. A total of 10 adults participated in this open-label pharmacokinetics study. The kinetics of an oral dose of 25 mg TLP was determined after a single oral dose; subjects were then given VPA 250 mg b.i.d. for 5 days, to determine steady state. On day 4, a repeat single oral dose of TLP 25 mg was administered and the pharmacokinetics analysis was repeated. At steady state, the trough plasma levels of VPA exceeded levels that were previously reported to inhibit drug metabolism. Under these conditions, VPA had no effect upon the kinetics of either TLP or its metabolite N-acetyl.

In an epilepsy study, a crossover add-on trial on TLP in patients with refractory partial seizures, 49 patients received TLP for 14 weeks[20]; 42 of the patients were on concomitant enzyme-inducing antiepileptic drugs (EIAEDs). In this study, the mean TLP dose was 60 mg t.i.d., with a mean final dose of 52 mg t.i.d; the mean plasma level was 155 mg/mL.

Dizziness was the most prominent adverse event, occurring in 52% of TLP-treated patients. Ataxia was the only other adverse event that occurred statistically more often than with placebo.

A randomized, double-blind, placebo-controlled, multicenter study has just been completed and review of the first 160 adult patients with refractory epilepsy has been conducted. To qualify, patients had to average at least three seizures per month (partial seizures with or without secondary generalization), with inadequate control of seizures on one to three antiepileptic drugs (AEDs). Patients were stratified according to their AED (inducers vs. non-inducers) and doses were escalated to either 35 mg t.i.d., a maximum of 50 mg t.i.d., or placebo. Once study drug escalation was completed, the patients remained on steady treatment for 12 weeks before having their TLP doses de-escalated to 0 mg. Patients who responded to treatment and wished to continue on TLP were enrolled in an open-label study and started on TLP at 25 mg t.i.d., titrating up to 100 mg t.i.d. Patients participating in this open-label study have been receiving TLP for the longest continuous period.

An interim analysis of this open-label study has been performed.[21] One-hundred patients were included in this interim analysis. Most patients tolerated a dose of 50 or 75 mg t.i.d. The overall responder rate, defined as the percentage of patients with ≥50% reduction in seizures from baseline, was 26.2%, and the median total seizure frequency reduction was 27.3%.

The responder rate was 39.6% for simple partial seizures, 33.8% for complex partial seizures, and 32.3% for partial seizures with secondary generalization. The most common side effects were dizziness (8.3%), headache (6.5%), and somnolence (4.6%).

TLP was discontinued in 17.6% of patients because of inadequate seizure control and in 7.4% because of side effects. Six patients were weaned off of their concomitant AEDs and were, at time of analysis, seizure-free on TLP monotherapy at doses ranging from 50 to 100 mg TID.

Talampanel appears to be effective and well-tolerated in adults with refractory complex partial seizures. In terms of tolerability in this population, TLP compares favorably with the newer AEDs.

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