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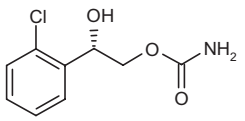
RWJ-333369

Antiepileptic Drug
Treatment of Migraine

YKP-509

Carbamic acid 2(*S*)-(2-chlorophenyl)-2-hydroxyethyl ester



$C_9H_{10}ClNO_3$
Mol wt: 215.6333
CAS: 194085-75-1
EN: 278595

Abstract

RWJ-333369 (YKP-509) is a novel, orally active neuromodulator. The compound displayed neuroprotective effects in a rat model of human temporal lobe epilepsy and reduced spontaneous motor seizures in rats with kainate-induced epilepsy. RWJ-333369 has shown linear pharmacokinetics in humans. Co-administration of RWJ-333369 with either valproate or lamotrigine revealed only minor pharmacokinetic drug interactions that were not considered to be clinically significant. Co-administration with carbamazepine, however, caused a reduction in RWJ-333369 C_{max} and AUC. Nevertheless, RWJ-333369 co-administered with any of these agents was generally well tolerated. It is currently undergoing phase II clinical trials for the treatment of epilepsy and migraine.

Synthesis

Esterification of (*S*)-(+)-2-chloromandelic acid (I) with MeOH/HCl gives the corresponding methyl ester (II), which after condensation with 2-methoxypropene (III) by means of HCl gas in toluene followed by neutralization with TEA yields the protected derivative (IV). Reduction of the ester intermediate (IV) with VENPURE™ B and A first and then with VENPURE™ C affords 2-(2-chlorophenyl)-2-(2-methoxypropoxy)ethanol (V), which after treatment with CDI in toluene and then with NH_4OH also in toluene affords the *O*-protected carbamate (VI). Compound (VI) is finally deprotected by means of HCl in toluene (1). Scheme 1.

Background

Epilepsy and migraine are both fairly common neurological disorders. The term “epilepsy” actually refers to a number of neurological conditions that make an individual more susceptible to recurrent unprovoked seizures. In epileptic disorders, the abnormal discharge of a hyperexcitable population of cortical neurons leads to the transient dysfunction of all or part of the brain, which in turn causes seizures. The clinical features of epilepsy include atypical EEG recordings and sudden brief seizures that may take the form of a brief stare, an unusual body movement, a change in awareness or a convulsion. Some individuals with epilepsy may experience an aura before the seizure occurs. Although the etiology of epilepsy remains unclear in most cases, seizure occurrence is sometimes triggered by environmental or dietary factors. In serious cases, epilepsy can evolve into status epilepticus, which can lead to brain damage and/or death. Current pharmacological treatment for epilepsy does not cure the disorder itself, although it can reduce the frequency, duration and severity of seizures, generally by increasing the brain seizure threshold in the epileptic focus (2).

Migraine, another common neurological disorder, is a severe, seriously debilitating and usually unilateral form of episodic headache that may also be preceded by an aura. Other symptoms such as nausea, vomiting and photophobia frequently occur simultaneously with headache during a migraine attack. The precise etiology and pathophysiology of migraine are unknown, although abnormal functioning of nerves and/or blood vessels of the head is thought to be involved. Like epilepsy, migraine with aura is thought to be related to a state of neuronal hyperexcitability. For this reason, anticonvulsant agents may also have a role in the prevention of migraine (3).

RWJ-333369 (YKP-509) is a novel neuromodulator with potent activity against electrically and chemically induced seizures in rodents. Although its mechanism of action has not yet been elucidated, RWJ-333369 appears to have potential as a treatment for epilepsy and migraine

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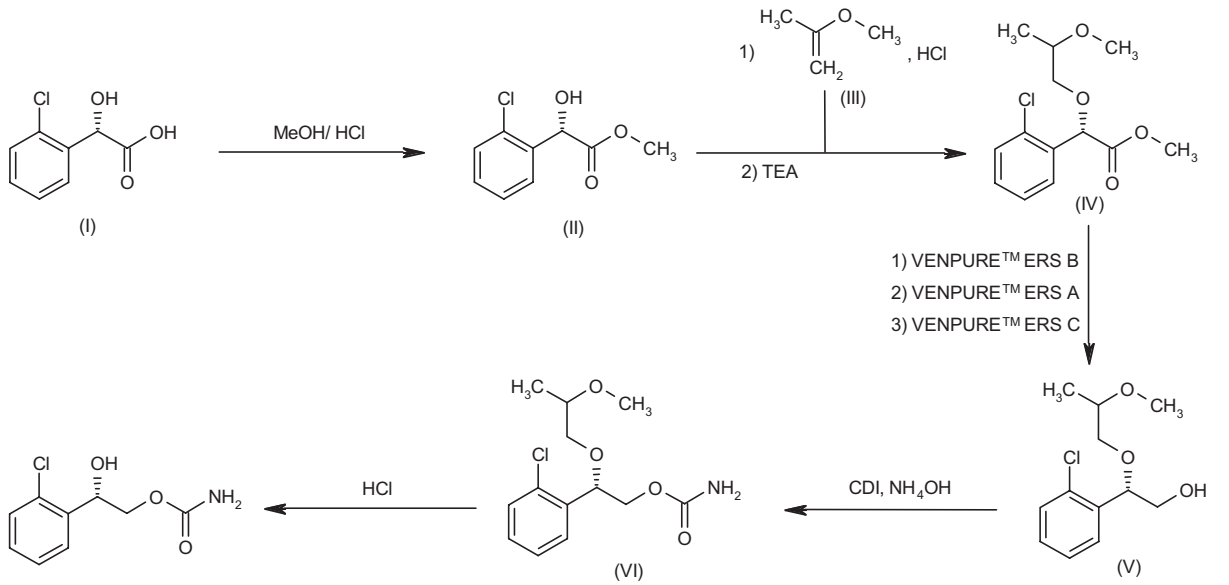
Scheme 1: Synthesis of RWJ-333369



and is currently undergoing phase II clinical evaluation for these disorders (4-7).

Preclinical Pharmacology

Many of the features of human temporal lobe epilepsy can be reproduced using the lithium-pilocarpine model. In this model, status epilepticus is induced in rats, and this phase is followed by a latent seizure-free phase, then a chronic phase in which spontaneous recurrent seizures occur, resulting in extensive damage to the hippocampus, thalamus, amygdala and ventral cortices. Using this model, RWJ-333369 (30, 60, 90 or 120 mg/kg) and diazepam (2.5 mg/kg, then 1.25 mg/kg), both injected i.p. at 1 and 8 h after the onset of status epilepticus, were compared. Neuronal damage assessed at day 14 revealed a reduced number of neurons in the hippocampus, ventral cortices, medial and lateral thalamus, and basolateral and medial amygdala in rats treated with diazepam. All doses of RWJ-333369 had protective effects on neurons in the CA1 area of the hippocampus, the dorsolateral part of the lateral thalamus and the basolateral amygdala. Additional neuroprotection was observed in the anterior part of the medial amygdala and layer II of the piriform cortex in rats receiving RWJ-333369 at 60 mg/kg. The highest dose levels (90 and 120 mg/kg) produced further neuroprotection in the posterior part of the medial amygdala, the ventrolateral part of the lateral thalamus, the mediodorsal thalamus and the deep layers of the piriform and ventral entorhinal cortices. Similar latencies of 12-15 days before rats developed spontaneous recurrent seizures were observed following treatment with diazepam and the lowest dose of RWJ-333369. In rats receiving the dose of 60 mg/kg, latency was 15 days in 7 rats, but 77 days in 3 rats. The latencies to spontaneous recurrent seizures in rats receiving the dose of 90 mg/kg were 15 days in 4 animals, 52 days in 2 rats and no seizures were seen in 5 rats after 5 months. In rats receiving the highest dose, the latencies were 13 days in 1 and 85 days in 4 animals and no seizures were seen in 4 rats after 5 months. The frequency of spontaneous recurrent seizures showed an inverse correlation to latency, while a direct correlation was observed for outcome and neuroprotection (8, 9).

A repeated-measures crossover protocol was used in rats with kainate-induced epilepsy to determine the efficacy of RWJ-333369 (1-30 mg/kg i.p.) against spontaneous motor seizures. At doses of 10 and 30 mg/kg, RWJ-333369 produced a significant and dose-dependent reduction in relative seizure frequency. Comparison of these results with data from a previous similar study with topiramate showed that treatment with RWJ-333369 led to a greater reduction in seizure frequency compared to treatment with topiramate (approximately 75% *vs.* 50%) (10).

Pharmacokinetics and Metabolism

The pharmacokinetics of RWJ-333369 are linear according to results from two double-blind, placebo-controlled, ascending-dose studies in healthy adult men. In the first study, 70 individuals received a single oral dose of RWJ-333369 (100, 250, 400, 750, 1000, 1250 or 1500 mg) or placebo. Results showed rapid absorption of the study drug, with C_{max} and $AUC_{0-\infty}$ values increasing in a dose-proportional manner over the dose range tested.

The following mean pharmacokinetic parameters were obtained: t_{max} = 1.3-2.7 h; $t_{1/2}$ = 11.5-13.9 h; CL/F = 2.87-3.67 l/h; and Vd/F = 52.1-66.2 l. A second study in 53 healthy volunteers assessed the safety and pharmacokinetics of repeated oral doses (100, 250, 500 or 750 mg) of RWJ-333369 administered twice daily for 1 week. Steady-state plasma concentrations were obtained after 3-4 days, and mean t_{max} occurred 1.3-1.8 h postdosing. The mean elimination half-life was 11.9-12.8 h and CL/F was 3.40-3.78 l/h. A dose-proportional increase in steady-state C_{max} and AUC_{0-12h} was observed in this study, with values showing a 2-fold increase on day 7 as compared to day 1. The main mechanism for RWJ-333369 elimination appeared to be metabolism prior to renal excretion. Five subjects receiving RWJ-333369 dropped out of the study, although only 3 of these were considered to do so for reasons possibly or probably related to the study drug (11).

Drug Interactions

The potential for pharmacokinetic drug interactions between RWJ-333369 and either valproate or lamotrigine was explored in two open-label, sequential-design studies in healthy adults. The first study, conducted in 24 subjects, found that the co-administration of valproate (21 doses of 500 mg twice daily) and RWJ-333369 (10 doses of 250 mg twice daily and 11 doses of 500 mg twice daily) had little effect on the C_{max} and AUC_{0-12h} values determined for RWJ-333369. Concomitant administration of RWJ-333369 (500 mg) with valproate caused a slight reduction in the valproate C_{max} and AUC_{0-12h} values. In both cases, these values were within the equivalence range of 80-125%. The second study investigated the co-administration of multiple doses of lamotrigine and RWJ-333369 in 24 healthy adults. In this study, co-administration of lamotrigine (50 mg twice daily for 34 doses) and RWJ-333369 (6 doses of 250 mg twice daily and 28 doses of 500 mg twice daily) had minimal effects on the C_{max} and AUC_{0-12h} of RWJ-333369. However, co-administration of RWJ-333369 (500 mg) with lamotrigine led to a reduction in lamotrigine C_{max} and AUC_{0-12h} values to levels that were slightly below the 80-125% equivalence range. Nevertheless, these changes were not considered to be clinically significant. The co-administration of RWJ-333369 with either valproate or lamotrigine was safe and well tolerated in these studies (12).

Another open-label, sequential-design study investigated possible phamacokinetic interactions between RWJ-333369 (250 mg twice daily for 5 days and 500 mg twice daily for 5 days) and carbamazepine (300 mg twice daily for 10 days) in 24 healthy adults. For RWJ-333369, C_{max} and AUC_{0-12h} values increased in a dose-proportional manner, whereas t_{max} values were independent of dose. Co-administration with RWJ-333369 had little effect on carbamazepine C_{max} or AUC_{0-12h} values. In contrast, co-administration with carbamazepine caused a 30% reduction in RWJ-333369 C_{max}, a 40% decrease in AUC_{0-12h}, a 60% increase in oral clearance and a 3-h reduction in $t_{1/2}$. Adverse events led 4 subjects receiving carbamazepine alone and 1 subject receiving both drugs to discontinue treatment. Concomitant treatment with RWJ-333369 and carbamazepine was generally well tolerated (13).

Sources

Johnson & Johnson (US); licensed worldwide from SK Bio-Pharmaceuticals.

References

1. Rey, M., Otten, T., Korey, D. (Ortho-McNeil Pharmaceutical, Inc.). *Process for preparing 2-(substituted phenyl)-2-hydroxyethyl carbamates*. CA 2471485, EP 1461309, WO 2003053916.

2. Prous Science Drug R&D Backgrounders: *Headache Disorders (online publication)*. Updated February 23, 2006.

3. Prous Science Drug R&D Backgrounders: *Epilepsy (online publication)*. Updated February 2, 2006.

4. *Safety and efficacy of 333369 in the treatment of partial epilepsy (NCT00228969)*. ClinicalTrials.gov Web Site 2005, December 8.

5. *A study of the effectiveness and safety of the investigational compound RWJ-333369 in patients with epilepsy (NCT00210522)*. ClinicalTrials.gov Web Site 2006, January 28.

6. *A study of the safety and preliminary effectiveness of the investigative compound RWJ-333369 in patients with epilepsy (NCT00210652)*. ClinialTrials.gov Web Site 2006, January 28.

7. *A study of the efficacy of RWJ-333369 in the prevention of migraine (NCT00109083)*. ClinicalTrials.gov Web Site 2005, December 8.

8. Francois, J., Ferrandon, A., Koning, E., Nehlig, A. *A new drug RWJ333369 protects limbic areas in the lithium-pilocarpine model (li-pilo) of epilepsy and delays or prevents the occurrence of spontaneous seizures*. Epilepsia 2005, 46(Suppl. 8): Abst C.04.

9. Francois, J., Ferrandon, A., Koning, E., Nehlig, A. *Epileptic outcome is correlated with protection in temporal cortices: Evidence from neuroprotection studies with a new drug, RWJ333369, in the lithium-pilocarpine model*. Epilepsia 2005, 46(Suppl. 6): Abst 048.

10. Grabenstatter, H.L., Dudek, F.E. *The use of chronic models in antiepileptic drug discovery: The effect of RWJ-333369 on spontaneous motor seizures in rats with kainate-induced epilepsy*. Epilepsia 2004, 45(Suppl. 7): Abst 2.016.

11. Yao, C., Choi, Y.M., Lee, S.J., Doose, D., Novak, G. *RWJ-333369 pharmacokinetics are linear following single and repeated oral administration in healthy adult men*. Epilepsia 2005, 46(Suppl. 8): Abst 2.301.

12. Chien, S.-C., Yao, C., Mertens, A., Verhaeghe, T., Solanki, B., Doose, D., Novak, G. *Lack of clinically significant pharmacokinetic drug interactions between RWJ-333369 and valproate or lamotrigine*. Epilepsia 2005, 46(Suppl. 8): Abst 2.245.

13. Chien, S.-C., Yao, C., Solanki, B., Verhaeghe, T., Doose, D., Novak, G. *Drug-drug interaction study between RWJ-333369 and carbamazepine in healthy adults*. Epilepsia 2005, 46(Suppl. 8): Abst 2.269.