Brivaracetam (UCB 34714)

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Summary: Brivaracetam (UCB 34714) is chemically related to levetiracetam (LEV, Keppra®). It possesses a binding affinity for the synaptic vesicle protein 2A (SV2A) ten-fold above that of LEV and also shows an ability to inhibit Na^+ channels. This correlates with a higher potency in suppressing epileptiform responses *in vitro* and a more potent and complete suppression of different seizure types in animals with an acquired or genetic epilepsy. Brivaracetam has been tested in a comprehensive safety pharmacology, toxicology, developmental toxicology, and genotoxicity program. It is of low acute toxicity, target organ for toxic effects is the hepatobiliary tract. Carcinogenicity studies are ongoing. Human pharmacology studies have shown that brivaracetam has a half-life of 8 h and nearly complete bioavailability. Brivaracetam is primarily metabolized via hydrolysis of the acetamide group and CYP2C8-mediated hydroxylation. Its metabolites are not pharmacologically active. Excretion of over 95% of the dose, including metabolites, occurs renally within 72 h. Healthy volunteer studies demonstrated a favorable tolerability profile. Treatment emergent adverse events were mild to moderate, mostly of CNS origin, and resolved within 24 hrs, with decreasing incidence after repeated intake. Drug-drug interaction studies with high dose of brivaracetam (400 mg/d) showed a dose-dependent increase of carbamazepine-epoxide levels. No significant interaction with low doses of phenytoin was observed at the same high dose levels of brivaracetam, and only a moderate pharmacokinetic interaction with an oral contraceptive, without impact on hormonal levels or ovulation, was observed. The pharmacokinetic profile of brivaracetam is unaltered in elderly subjects or those with impaired renal function. Clearance of brivaracetam is reduced in patients with hepatic insufficiency. In the photoparoxysmal response model in patients with photosensitive epilepsy brivaracetam was effective at all tested doses (10 – 80 mg) in reducing or abolishing EEG discharges evoked by a photic stimulus. Phase 2 studies in patients with refractory partial onset seizures have recently been completed.
Key Words: Brivaracetam, UCB 34714, synaptic vesicle protein 2A, SV2A

INTRODUCTION

The synaptic vesicle protein 2A (SV2A) is a widely distributed CNS protein believed to be involved in the coordination of synaptic vesicle exocytosis and neurotransmitter release.[1] Binding affinity to SV2A of the antiepileptic drug levetiracetam (LEV, Keppra®), as well as of a series of LEV analogues, correlates highly with the seizure protection afforded by these compounds in animal models of epilepsy.[2] The novel SV2A ligand brivaracetam ((2*S*)-2-[(4*R*)-2-oxo-4-propylpyrrolidinyl] butanamide) was identified in an extensive drug discovery program aimed at enhancing the well-established antiepileptic properties of LEV. It is a 2-pyrrolidone derivative structurally related to LEV with a mol weight of 212 and displays a markedly higher affinity (pK_i = 7.1) than LEV (pK_i = 6.1) for SV2A.[3] In addition to its affinity for SV2A it has shown inhibitory effects on voltage-dependent Na^+-currents in rat cortical neurons in culture.[4]

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PHARMACOLOGY

Brivaracetam was tested *in vitro* in rat hippocampal slices following perfusion with a high potassium-low calcium-containing fluid at concentrations of 1–10 μM. In this model, brivaracetam significantly suppressed evoked epileptiform responses (population spikes, PSs) recorded in the CA3 area. Active concentrations lay 10-fold below those of LEV (3.2 μM vs 32 μM). It is of note that brivaracetam at the same concentrations also reduced the occurrence of spontaneous bursts, while LEV is inactive against this drug-refractory marker of epileptiform activity.[5,6]

Brivaracetam has been extensively studied in *in vivo* models of epilepsy and convulsion. The corneally kindled mouse is a model for partial epilepsy. In this para-

digm, brivaracetam at concentrations several-fold below those necessary with LEV protected animals from secondarily generalized motor seizures (ED50 values = 1.2 vs 7.3 mg/kg, i.p.). In a further model of focal epilepsy, the amygdala-kindled rat, brivaracetam provided a more profound suppression of both motor seizure severity and after-discharge duration than LEV. The activity of brivaracetam was also investigated in models of generalized seizures. Mice genetically susceptible to audiogenic seizures were more potently protected from clonic convulsions with brivaracetam than with LEV (ED50 values = 2.4 vs. 30 mg/kg, i.p.). In an experimental model of absence epilepsy, the genetic absence epilepsy rat from Strasbourg (GAERS), a more complete suppression of spike-wave-discharges with brivaracetam than with LEV was observed.[7]

In the same corneal kindling model, chronic pretreatment prior to corneal stimulation with LEV or 10-fold lower doses of brivaracetam 2 x daily (1.7-54 mg/kg i.p. *versus* 0.21-6.8 mg/kg i.p.) led to a similar suppression of kindling development.[8] Most notably, the cessation of treatment with continued corneal stimulation resulted in a more significant and persistent inhibition of the kindling process than that seen with LEV.

In order to assess the anticonvulsant properties of brivaracetam in an acute seizure model, the activity of the compound against partially drug-resistant self-sustaining status epilepticus (SSSE) in rats was studied. This model has shown that stimulation of excitatory pathways can create reverberating limbic circuits in which seizures are self-sustaining and thereby induce damage to the brain.[7] This process, once set in motion, is refractory to standard anticonvulsants such as diazepam and, at a later point, phenytoin.[9] SSSE was induced by perforant path stimulation (PPS) in adult male rats. The cumulative duration of active seizures was reduced dose-dependently to 11% and 0.8% of controls at 20 and 300 mg/kg, respectively. This activity compares favorably to the result of 35% of controls achieved with 200 mg/kg of LEV and 15% of controls with 10 mg/kg of diazepam. The combination of diazepam (1 mg/kg) and brivaracetam (1 mg/kg) reduced the duration of active seizures to 3% of controls, while either drug alone had little effect at these doses. This experiments showed potent anticonvulsant activity of the compound in an animal model of status epilepticus.[10]

SAFETY PHARMACOLOGY AND TOXICOLOGY

The acute oral toxicity of brivaracetam has been shown to be low in mice, rats, and dogs, with transient CNS effects generally occurring at doses of 100 mg/kg or above in a dose-dependent fashion. These effects regressed under continuous treatment within a few days. Significant cardiovascular, respiratory, or gastrointestinal effects have not been observed (UCB, data on file). The maximum nonlethal oral single dose in the rat lay above 1000 mg/kg and a no-effect level of 500 mg/kg was established in male and female rats based on clinical signs.

Chronic toxicity was assessed in dogs, rats and monkeys. The non- observed adverse effect level (NOAEL) after 26 weeks of repeated administration in dogs was 15 mg/kg/day with an area under the curve (AUC) of 34.7 μg./mL. At higher doses hepatobiliary adverse effects were noted in these animals. Overall, the NOAEL in the rat after 26 weeks of oral dosing was considered to be 450 mg/kg/day in both males and females (AUC of 257 and 464 μg.h/mL respectively), when male-rat-specific hyaline droplet nephropathy, of no consequence for man, is set aside. 39 weeks of chronic administration of brivaracetam in monkeys allowed for the identification of the NOAEL at 900 mg/kg/day (AUC of 2351 μg.h/mL).

No adverse effects on fertility and early embryonic development were detected up to the highest tested oral dose of 400 mg/kg/day. No effects on pregnancy or on fetal development occurred at the highest tested dose of 600 mg/kg/day in a fetal development study in the rat. The fetal/developmental NOAEL in the rabbit was identified at a dose of 120 mg/kg/day.

Genotoxicity was investigated in a panel of studies (Ames bacterial mutation, mouse lymphoma *in vitro* mammalian cell mutation, Chinese hamster ovary *in vitro* chromosomal aberration and an *in vivo* rat micronucleus chromosomal aberration assay). Taken together these studies suggested that brivaracetam is neither mutagenic nor clastogenic.

Carcinogenicity studies are currently ongoing (UCB, data on file).

CLINICAL PHARMACOKINETICS

Bioavailability of brivaracetam is rapid and almost complete following oral administration. The drug shows linear pharmacokinetics over a dose range from 10 to 600 mg. The metabolic clearance of brivaracetam is increased in a time-dependent fashion at supratherapeutic doses; a steady state is reached within 1 week of repeated administration. Plasma protein binding is weak ($\leq$ 20%), the volume of distribution, 0.6 l/kg, being close to that of total body water. The terminal elimination half-life of brivaracetam is approximately 8 h and does not vary with the administered dose.[11]

A pharmacoscintigraphy study (UCB, data on file) investigated the regional absorption profile of brivaracetam. Brivaracetam was consistently absorbed throughout the GI tract, as evidenced by the relative AUC (100%=stomach) of 101, 98, and 97% following delivery in the proximal jejunum, distal jejunum, and ascending colon respectively.

A food interaction study[12] in healthy volunteers showed the lack of effect of a high fat meal on the extent of absorption (fed/fasted AUC ratio = 1.00). The absorption rate was slowed down, as evidenced by a C_{max} reduction of approximately 50% and T_{max} increase from 0.5 to 3.5 h.

The major metabolic pathways of brivaracetam include hydrolysis of the acetamide group, CYP2C8-mediated hydroxylation, and a combination of these pathways. No pharmacological activity of the resulting metabolites has been shown. Elimination of brivaracetam is mainly by metabolism. Renal clearance of the parent drug is low at 0.06 ml/min/kg, whereas the metabolites have a high renal clearance. More than 95% of a radioactive dose is recovered in urine within 72 h.

DRUG INTERACTIONS

In vitro, brivaracetam inhibits epoxide hydrolase and, to a lesser extent, CYP3A4 and 2C19, and is a weak inducer of CYP3A4.

The interaction potential of brivaracetam with carbamazepine (CBZ) was investigated in a formal interaction study in nine patients with epilepsy on stable doses with CBZ. Plasma levels were slightly reduced by co-administration with brivaracetam at 400 mg/d; carbamazepine-epoxide (CBZE) levels, on the other hand, were increased dose-dependently. However, the ratio of the metabolite and the parent drug (CBZE/CBZ) remained in the reported range under current clinical use.[13] These findings confirm prior data in healthy volunteers, in which a reduction of the AUC of CBZ by 13% and an increase of CBZE of 2.5-fold was observed under repeated b.i.d. administration of a very high dose of 200 mg. A dose of 400 mg/d lies most likely severalfold above the dose considered for clinical use in patients suffering from epilepsy.

Interaction with phenytoin (PHT), which is metabolized primarily by CYP 2C9 and secondarily by CYP 2C19, was assessed in 20 healthy male volunteers after 10 days of treatment with 400 mg/d of brivaracetam in b.i.d. administration. The C_{max} and the AUC of a single dose of 600 mg PHT were decreased slightly from baseline after brivaracetam treatment, but did remain within the confidence interval of 80–125%.

An interaction study of brivaracetam at the same high dose of 400 mg/d b.i.d. with an oral contraceptive, showed no impact on the suppression of ovulation, although a moderate reduction of the estrogen and progestin components of the contraceptive was reported.

The pharmacokinetic profile of brivaracetam in elderly and renally impaired subjects was similar to that of healthy volunteers (UCB, data on file).

In an open-label study, subjects with chronic liver disease were compared to healthy subjects (UCB, data on file). The apparent total body clearance of brivaracetam was reduced by 24%, 32%, and 35% in subjects with respectively mild, moderate, and severe hepatic impairment. The plasma half-life of brivaracetam (9.8 h in normal subjects) was prolonged to 14.2 h, 16.4 h, and 17.4 h, respectively. In conclusion, exposure to brivaracetam appeared to be increased about 50-60% in subjects with hepatic function impairment.

Further drug-drug interaction studies and studies in special populations are currently ongoing.

EFFICACY DATA

The antiepileptic potential of brivaracetam was studied in a human model of epilepsy, the photoparoxysmal response (PPR) paradigm. Patients with photosensitive epilepsy underwent intermittent photic stimulation (IPS) at varying frequencies, which elicited photoparoxysmal EEG discharges. Measurement of PPR occurred before and serially up to 72 h after the administration of a single dose of 80, 40, 20, or 10 mg of brivaracetam or of placebo.

Only partial or no reduction of the PPR was observed after administration of placebo. After treatment with brivaracetam, important reductions or abolishment of response was observed in all evaluable patients at all tested doses. Three out of four patients showed complete suppression of photoparoxysmal EEG discharges even at the lowest dose of 10 mg. Duration of effect was longer in patients who received 80 mg (median 59.5 h) than in those treated with a lower dose (medians from 27.0 to 29.3 h). In addition to demonstrating effective suppression of photoparoxysmal EEG discharges in patients with photosensitive epilepsy, these data suggest an efficacious dose range below that used in prior clinical pharmacology studies, and thus possibly the clinical irrelevance of the dose-dependent finding on pharmacokinetic interaction with other drugs.[14]

TOLERABILITY

Single oral doses of brivaracetam, up to 1000 mg and repeated oral doses up to 800 mg/d b.i.d., were well-tolerated in healthy volunteers and in patients. Treatment-emergent adverse events were mostly CNS-related and transient, and their intensity was usually mild or moderate. Repeated intake of the drug reduced their incidence. Clinical laboratory examinations, vital signs, ECG, and physical examinations did not provide evidence for significant effects of brivaracetam.

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