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Human abuse potential of brivaracetam in healthy recreational central nervous system depressant users

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ABSTRACT

Background: Brivaracetam is a new antiepileptic drug indicated for adjunctive treatment of focal seizures in adults at a dose of 50–200 mg/day taken in two equal doses. The objective of this study was to evaluate the abuse potential of brivaracetam compared with alprazolam (positive control), placebo, and levetiracetam.
Methods: This was a randomized, double-blind, triple-dummy, crossover study in healthy male and female recreational central nervous system (CNS) depressant users aged 18–55 years, who could distinguish between the subjective effects of alprazolam 2 mg and placebo. All participants received single doses of brivaracetam (50 [therapeutic dose], 200, 1000 mg [supratherapeutic doses]), alprazolam (1.5, 3 mg), placebo, and levetiracetam (4000 mg) in random order each separated by 7–10 days. Subjective Visual Analogue Scales (VAS) and Addiction Research Center Inventory (ARCI) scales were completed at intervals up to 24 h postdose. Primary endpoints were Drug Liking (at this moment) VAS, Overall Drug Liking VAS, Feeling High VAS, and ARCI Pentobarbital Chlorpromazine Alcohol Group (PCAG, sedation) maximum effect (E_{max}). Maximum effect values on each scale were analyzed using a mixed-effect model (per protocol population, N = 44).
Results: The maximum effect for both alprazolam doses was significantly greater versus placebo for six designated endpoints, confirming study validity. Drug Liking (at this moment) VAS E_{max} was significantly lower for brivaracetam 50 mg than alprazolam (both doses); there were no significant differences between brivaracetam 200 mg and alprazolam (both doses), and brivaracetam 1000 mg and alprazolam 1.5 mg. Brivaracetam 1000 mg (supratherapeutic single dose) had significantly higher Drug Liking (at this moment) VAS E_{max} than alprazolam 3 mg. Overall, Drug Liking VAS E_{max} for brivaracetam 50 and 200 mg was not significantly different from alprazolam (both doses). Brivaracetam 1000 mg had significantly higher Overall Drug Liking VAS E_{max} than alprazolam 1.5 mg, but was not significantly different from alprazolam 3 mg. Feeling High VAS E_{max} was lower versus alprazolam with brivaracetam 50 and 200 mg, while brivaracetam 1000 mg was comparable with alprazolam (both doses). Addiction Research Center Inventory PCAG E_{max} for brivaracetam (all doses) was significantly lower than alprazolam (both doses). On the secondary/supportive endpoints, compared with alprazolam, brivaracetam had fewer positive effects (ARCI Morphine Benzedrine Group [euphoria]; Good Drug Effects VAS [50 mg]) and fewer negative effects (Bad Drug Effects VAS; ARCI Lysergic Acid Diethylamide [dysphoria]). Brivaracetam was not significantly different from alprazolam for Take Drug Again VAS (50, 200 mg). For most endpoints, brivaracetam (50–200 mg) was not significantly different from levetiracetam (4000 mg).
Conclusion: This study in healthy recreational CNS depressant users showed that single doses of brivaracetam 50 mg (therapeutic single dose) had lower sedative, positive, and negative drug effects than alprazolam, while brivaracetam 200 and 1000 mg (supratherapeutic single doses) were more similar to alprazolam. The subjective profile of brivaracetam appeared to be similar to that of levetiracetam, but further evaluation using a range of levetiracetam doses would be needed to confirm similar abuse potential.

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ARTICLE IN PRESS

1. Introduction

Brivaracetam is a new, approved antiepileptic drug (AED) for adjunctive treatment of focal (partial onset) seizures in adults, at a therapeutic dose range of 50–200 mg/day taken in two equal doses. Brivaracetam is a selective, high-affinity ligand for synaptic vesicle protein 2A (SV2A), with a binding affinity approximately 15- to 30-fold higher than that of levetiracetam, another SV2A ligand [1]. Compared with levetiracetam, brivaracetam has a higher potency and shows more complete seizure suppression in a wide range of animal models of epilepsy [2].

In three fixed-dose Phase III studies, patients with epilepsy received adjunctive brivaracetam or placebo, without up-titration [3–5]. The most frequently reported treatment-emergent adverse events (TEAEs) in a pooled analysis of the therapeutic dose range were somnolence (brivaracetam vs. placebo, 15.2% vs. 8.5%), dizziness (11.2% vs. 7.2%), headache (9.6% vs. 10.2%), and fatigue (8.7% vs. 3.7%) [6], consistent with central nervous system (CNS) activity. The guidelines of US Food and Drug Administration (FDA) indicate that new drugs with CNS activity are likely to require a thorough assessment of their abuse potential, including human studies [7]. Findings from human abuse potential studies contribute to decisions regarding labeling and scheduling of new drugs. Levetiracetam has demonstrated signals that suggest low-level abuse potential in subjects with a history of drug abuse, although it is not thought to be associated with actual abuse in the marketplace [8].

The primary objective of this study was to evaluate the abuse potential of single oral doses of brivaracetam compared with alprazolam (positive control), a Schedule IV drug, and placebo. Secondary objectives were to compare the abuse potential of brivaracetam with that of levetiracetam and to further evaluate the pharmacokinetics, safety, and tolerability of brivaracetam. Experienced recreational users of CNS depressants were selected for participation as they would be expected to readily identify the effects of this class of drugs, and thus, provide accurate information on the likelihood of abuse [9]. Brivaracetam was tested at both therapeutic (50 mg) and supratherapeutic (200, 1000 mg) single doses.

2. Methods

This randomized, double-blind, triple-dummy Phase I study was conducted at DecisionLine Clinical Research Corporation, Ontario, Canada (now known as INC Research, North Carolina, USA) between November 2008 and March 2009. The study was conducted in accordance with the International Conference on Harmonization notes for Guidance on Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the Quebec Board of Institutional Review Board Services, Ontario, Canada, and written informed consent was obtained from all participants before enrollment.

2.1. Participants

This study recruited male and female subjects aged 18–55 years, with body mass index (BMI) of 18–32 kg/m^2 and weight ≥50 kg, and who were in good physical and mental health. Eligible participants had a history of, or current, recreational CNS depressant (e.g., benzodiazepines, barbiturates, cannabis, flunitrazepam, gamma-hydroxybutyrate) use, defined as ≥10 lifetime experiences including ≥1 in the previous 3 months. Key exclusion criteria included a history of, or current, substance dependence according to DSM-IV criteria; a history of, or current, treatment for substance use disorder; excessive alcohol use (male: >28 units/week, female: >21 units/week) in the previous month; and current smoker (≥20 cigarettes per day or equivalent) who was unable to abstain for ≥10 h. Drug treatment (apart from study medication, contraceptives, vitamins, minerals, and occasional acetaminophen) was not permitted during the 2 weeks prior to screening (or 2 months for enzyme inhibitors or inducers) and throughout the study. Negative urine drug screen and alcohol breath tests were required at screening and prior to each dose of study medication. At the discretion of the investigator, positive tests for cannabinoids and benzodiazepines may have been allowed because of their long half-lives.

2.2. Study design

The study design was consistent with the guidelines for the assessment of abuse potential available at the time of the study [9–11]. The study comprised a qualification phase, a treatment phase, and a final assessment 7 days after the last dose of study medication.

The qualification phase was conducted to ensure that only participants who liked the effects of alprazolam, and could clearly distinguish between alprazolam and placebo, entered the treatment phase. During the qualification phase, participants received single doses of alprazolam 2 mg or placebo administered in random order on 2 consecutive days at least 24 h apart. Participants were required to meet the following criteria in order to be eligible for the treatment phase: maximum effect (E_{max}) in response to alprazolam greater than placebo for Drug Liking, Overall Drug Liking, and Feeling High Visual Analogue Scales (VAS) and Addiction Research Center Inventory (ARCI) Pentobarbital Chlorpromazine Alcohol Group (PCAG; sedation) scale; responses consistent with the known effects of alprazolam; ability to tolerate alprazolam 2 mg; and general behavior suggestive that the participant would be able to successfully complete the study. Subjective judgments were made by two independent raters at the study center, with a third rater in the event of a disagreement.

During the treatment phase, eligible participants received single, oral doses of brivaracetam (50, 200, 1000 mg), alprazolam (1.5, 3 mg), placebo, and levetiracetam (4000 mg) in random order each separated by 7–10 days. Randomization of the treatment sequences was drawn up according to a Williams square design with two 7 × 7 Latin squares. Three participants were allocated to each of the 14 treatment sequences (N = 42). Participants remained in the study center from the day before each dose of study medication to approximately 24 h postdose.

2.3. Pharmacodynamic assessments

Participants completed subjective VAS, as described previously [12], and ARCI [13] scales (Table 1) at intervals of up to 24 h following each dose of study medication using validated computer software (Scheduled Measurement System, DecisionLine Clinical Research Corporation, Toronto, Ontario, Canada). The scales used are standard measures for this type of study and are consistent with current FDA guidelines [7]. The following scales were completed at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h postdose: Drug Liking VAS, Any Drug Effects VAS, Good Drug Effects VAS, Bad Drug Effects VAS, Feeling High VAS, Dizziness VAS, ARCI PCAG, ARCI Morphine Benzedrine Group (MBG; euphoria), ARCI Lysergic Acid Diethylamide (LSD; dysphoria), ARCI Amphetamine (stimulation and euphoria), and ARCI Benzedrine Group (BG; attention and euphoria). Feeling High VAS and Dizziness VAS were also completed predose. Overall Drug Liking VAS and Take Drug Again VAS were completed at 12 and 24 h postdose.

For each scale, E_{max} over the 24 h following each dose of study medication was determined. Primary endpoints were defined as E_{max} for Drug Liking VAS, Overall Drug Liking VAS, Feeling High VAS, and ARCI PCAG. Secondary endpoints were Take Drug Again VAS, Any Drug Effects VAS, Good Drug Effects VAS, Bad Drug Effects VAS, ARCI MBG, and ARCI LSD. Dizziness VAS, ARCI Amphetamine, and ARCI BG were regarded as supportive endpoints.

2.4. Pharmacokinetic assessments

Blood samples were collected for analysis of plasma concentrations of brivaracetam, levetiracetam, and alprazolam predose, and at 1, 2, 3, 6, 8, 12, and 24 h postdose. Maximum plasma concentration (C_{max}),

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