Epilepsy & Behavior 62 (2016) 267–275

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Randomized double-blind comparison of cognitive and EEG effects of lacosamide and carbamazepine

Kimford J. Meador [a,*], David W. Loring [b,c], Alan Boyd [d], Javier Echauz [e], Suzette LaRoche [b,1], Naymee Velez-Ruiz [b,2], Pearce Korb [f], William Byrnes [g], Deanne Dilley [g], Simon Borghs [h], Marc De Backer [i], Tyler Story [j,3], Peter Dedeken [i], Elizabeth Webster [g]

[a] Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA
[b] Department of Neurology, Emory University, Atlanta, GA, USA
[c] Department of Pediatrics, Emory University, Atlanta, GA, USA
[d] CNS Vital Signs, Morrisville, NC, USA
[e] JE Research, Inc., Alpharetta, GA, USA
[f] Department of Neurology, University of Colorado, Denver, CO, USA
[g] UCB Pharma, Raleigh, NC, USA
[h] UCB Pharma, Slough, UK
[i] UCB Pharma, Brussels, Belgium
[j] UCB Pharma, Atlanta, GA, USA

ARTICLE INFO

Article history:
Received 19 May 2016
Revised 1 July 2016
Accepted 2 July 2016
Available online xxxx

Keywords:
Lacosamide
Carbamazepine
Cognition
EEG
Neuropsychology

ABSTRACT

Differential effectiveness of antiepileptic drugs (AEDs) is more commonly determined by tolerability than efficacy. Cognitive effects of AEDs can adversely affect tolerability and quality of life. This study evaluated cognitive and EEG effects of lacosamide (LCM) compared with carbamazepine immediate-release (CBZ-IR). A randomized, double-blind, double-dummy, two-period crossover, fixed-dose study in healthy subjects compared neuropsychological and EEG effects of LCM (150 mg, b.i.d.) and CBZ-IR (200 mg, t.i.d.). Testing was conducted at screening, predrug baseline, the end of each treatment period (3-week titration; 3-week maintenance), and the end of each washout period (4 weeks after treatment). A composite Z-score was derived for the primary outcome variable (computerized cognitive tests and traditional neuropsychological measures) and separately for the EEG measures. Other variables included individual computer, neuropsychological, and EEG scores and adverse events (AEs). Subjects included 60 healthy adults (57% female; mean age: 34.4 years [SD: 10.5]); 44 completed both treatments; 41 were per protocol subjects. Carbamazepine immediate-release had worse scores compared with LCM for the primary composite neuropsychological outcome (mean difference = 0.33 [SD: 1.36], $p = 0.011$) and for the composite EEG score (mean difference = 0.92 [SD: 1.77], $p = 0.003$). Secondary analyses across the individual variables revealed that CBZ-IR was statistically worse than LCM on 36% (4/11) of the neuropsychological tests (computerized and noncomputerized) and 0% of the four EEG measures; none favored CBZ-IR. Drug-related AEs occurred more with CBZ-IR (49%) than LCM (22%). Lacosamide had fewer untoward neuropsychological and EEG effects and fewer AEs and AE-related discontinuations than CBZ-IR in healthy subjects. Lacosamide exhibits a favorable cognitive profile.

Abbreviations: AEDs, antiepileptic drugs; LCM, lacosamide; CBZ-IR, carbamazepine immediate-release; EEG, electroencephalogram; AEs, adverse events; C-SSRS, Columbia-Suicide Severity Rating Scale; MCG, Medical College of Georgia paragraph memory; SDMT, Symbol Digit Modalities Test; POMS, Profile of Mood States; ABNAS, A-B Neuropsychological Assessment Schedule; TEAEs, treatment-emergent AEs.

* Corresponding author at: Department of Neurology & Neurological Sciences, Stanford University School of Medicine, 213 Quarry Road, MC 5979, Palo Alto, CA 94304-5979, USA. Tel.: +1 650 725 6648; fax: +1 650 721 4865.

E-mail addresses: kmeador@stanford.edu (K.J. Meador), dloring@emory.edu (D.W. Loring), aboyd@cnsvs.com (A. Boyd), echauz@ieee.org (J. Echauz), Suzette.LaRoche@msj.org (S. LaRoche), nxv146@med.miami.edu (N. Velez-Ruiz), pearce.korb@ucdenver.edu (P. Korb), Bill.Byrnes@ucb.com (W. Byrnes), Deanne.Dilley@ucb.com (D. Dilley), Simon.Borghs@ucb.com (S. Borghs), Marc.DeBacker@ucb.com (M. De Backer), TylerJStory@gmail.com (T. Story), Peter.Dedeken@ucb.com (P. Dedeken), Elizabeth.Webster@ucb.com (E. Webster).

[1] Present address: Mission Health, Asheville, NC, USA.
[2] Present address: University of Miami, Miami, FL, USA.
[3] Present address: GW Pharmaceuticals, Atlanta, GA, USA.

http://dx.doi.org/10.1016/j.yebeh.2016.07.007
1525-5050/

1. Introduction

Lacosamide (LCM) is a unique antiepileptic drug (AED) exerting its activity predominantly by selectively enhancing slow sodium channel inactivation [1]. Lacosamide has been shown to be efficacious as adjunctive therapy and monotherapy for focal epilepsy in four randomized clinical trials [2–5]. Differential side effect profiles of AEDs play an important role in therapeutic decisions for the treatment of epilepsy. Lacosamide is generally well-tolerated, but it has shown dose-dependent central nervous system side effects [6]. A retrospective open-label study of 44 patients treated with LCM compared with 11 patients treated with lamotrigine and 15 patients treated with topiramate found that the cognitive side effect profile of LCM was comparable with that of lamotrigine and superior to that of topiramate [7]. However, LCM's neuropsychological effects have not been assessed in a prospective, double-blind, randomized design. This study employed such a design to compare the cognitive and electroencephalogram (EEG) effects of LCM and carbamazepine immediate-release (CBZ-IR) in healthy adults. The study design is similar to multiple prior studies [8–15]. It was conducted in healthy adults rather than patients with epilepsy to avoid the confounding effects that changes in seizure frequency can produce on cognitive functions and to allow a crossover design with detailed testing, which reduces sample size and increases power by controlling for individual differences in cognitive abilities but is difficult to use in patients with epilepsy because of seizures [16].

2. Methods

2.1. Study design

This was a randomized, double-blind, double-dummy, 2-period crossover study to compare differences in neuropsychological parameters in healthy subjects after administration of 300 mg/day of LCM or 600 mg/day of CBZ-IR (eFig. 1). Target dosages were chosen to be typical therapeutic dosages used in clinical practice. Carbamazepine immediate-release was employed as the comparator drug to allow results to be compared with multiple prior studies in which it was employed [8,10,11,14]. Subjects were enrolled to participate in the crossover study to receive immediate-release formulations of both treatments (LCM and CBZ-IR) in a randomized order during the 2 study treatment periods (Treatment Period 1 and Treatment Period 2) with a total of 10 visits over approximately 23 weeks between May 2012 and February 2014. An Interactive Web Response System (IWRS) was used for assigning eligible subjects to a treatment regimen based on a predetermined randomization schedule provided by UCB. The randomization was produced by a UCB biostatistician who was otherwise not involved in this study. The IWRS was responsible for issuing subject kits of the study medication according to the visit schedule. A 21-day screening period was followed by Treatment Period 1 which lasted 6 weeks (21-day Titration Period and 21-day Maintenance Period). Completing subjects transitioned to a 28-day Taper/Washout Period, during which their first AED was tapered over 4 days followed by a 24-day Washout Period. Upon completion of the Taper/Washout Period, subjects began Treatment Period 2. The durations, procedures, and assessments for Treatment Period 1 were repeated for Treatment Period 2. For subjects who completed the study, an End-of-Study Visit was conducted approximately 24 days after the final administration of the study medication. Dose reduction was not allowed during the Titration or Maintenance Periods in Treatment Period 1 or Treatment Period 2. Subjects who were not able to tolerate 300 mg/day of LCM or 600 mg/day of CBZ-IR were discontinued from the study and completed a termination visit after approximately 14 days. The protocol was amended to include a second clinical site to expand subject eligibility requirements by changing the BMI from 19–28 to 18–35, and to allow rescreening of subjects who were not randomized.

2.2. Standard protocol approvals, registrations, and patient consents

The study protocol, amendments, and subject informed consent were reviewed by the Midlands Independent Institutional Review Board (IRB) and Emory University IRB. Data were collected at the 2 participating sites, Quintiles Phase One Services, LLC (Overland Park, KS) and Emory University (Atlanta, GA), respectively. Subject informed consent was obtained and documented in accordance with local regulations and the principles of the Declaration of Helsinki. The clinical study was registered at www.clinicaltrials.gov (SP0998; NCT01530022).

2.3. Subjects

Following the screening period, healthy male and female paid subjects (18–55 years of age) were randomized (1:1) to 1 of 2 treatment sequences: LCM/CBZ-IR or CBZ-IR/LCM. Eligible subjects had a body mass index (BMI) of 18–35 kg/m^2 and were in good health without a history of neurological or psychological diseases. Exclusion criteria consisted of the following: a score of ≤70 on the Peabody Picture Vocabulary Test [17]; a lifetime history of suicide attempt or suicidal ideation in the past 6 months (Columbia-Suicide Severity Rating Scale [C-SSRS]) [18]; a known hypersensitivity to any components of LCM or CBZ-IR or any concomitant medications, herbal supplements, or foods known to affect LCM or CBZ metabolism or have significant effects on cognition; a history of alcohol or drug abuse in the last 2 years; a positive drug urine screen; or caffeine intake of >600 mg/day or smoking >10 cigarettes/day. During the study, subjects were not allowed to consume alcohol or take over-the-counter medications in the 72 h preceding cognitive and behavioral testing.

2.4. Study medications

Study medications were administered three times daily in a double-dummy fashion, with matching capsules or tablets for each drug. The accompanying packaging was identical in appearance so that neither the investigator nor the subject was able to tell whether the subject was receiving LCM or CBZ-IR. The doses of 300 mg/day of LCM (150 mg, b.i.d. with midday placebo dose) and 600 mg/day of CBZ-IR (200 mg, t.i.d.) were chosen because they represent the midrange effective doses (LCM approved doses are 200–400 mg/day [19], CBZ-IR approved doses are 400–1200 mg/day [20]). A mean (±SD) daily dose of 567 (110) mg/day of CBZ-IR yielded a midrange anticonvulsant blood level in healthy adults [14]; thus, 200 mg three times daily (600 mg/day) was used in the current study as a midrange dose.

During each Titration Period, LCM and CBZ-IR were titrated to a maintenance dose of 300 mg/day of LCM and 600 mg/day of CBZ-IR by Week 3 with increments of 100 mg/week and 200 mg/week, respectively. During the Taper/Washout Period, both treatments were tapered over 4 days, followed by a 24-day Washout Period.

Study medication compliance was assessed during each treatment period separately. Compliance was computed at each visit by determining the number of tablets and capsules taken relative to the number of tablets and capsules that should have been taken according to the protocol.

2.5. Neuropsychological and electroencephalogram (EEG) outcome variables

Testing for these measures was conducted during the Screening Period and repeated at the Beginning of Treatment Period 1 (i.e., the Baseline), End of Treatment Period 1, End of Washout Period, End of Treatment Period 2, and End of Study. The first test session in the screening period was to familiarize subjects with the procedures and to reduce test–retest effects. Results from the first test session were not analyzed. The mean nondrug score for each component was calculated by averaging the nondrug scores across the Beginning of Treatment Period 1 (i.e., the Baseline), End of Washout Period, and