for by differences in bodyweight and concomitant use of inducer AEDs. Since the identified covariates had a modest influence on pharmacokinetic parameters, BRV is deemed to have a highly predictable exposure in individual subjects. Results suggest that no dose adjustment is required.

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LEVETIRACETAM, A NEW OPTION TREATMENT FOR CREUTZFELDT-JACOB DISEASE

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Rationale: Levetiracetam showed to be effective in the treatment of myoclonic seizures. The aim of this study is to evaluate the efficacy of levetiracetam (LEV) in the treatment of myoclonus in Creutzfeldt-Jacob disease (CJD).

Methods: Since 2003 we treated with LEV 6 patients with CJD who presented, initially or during the course of the disease, mild, moderate or intense myoclonus involving subcontinuously face and arms.

Patients were three men (mean age at onset 56 yrs) and three women (mean age at onset 61 yrs).

Three patients had a sporadic and three a genetic form of CJD. Five patients had a polymorphism at codon 129 Met/Met and only one had no polymorphism but showed E200K gene mutation of PRP.

EEG showed in two cases periodic slow waves complex, in two frontal intermittent rythmic delta activity and in two diffuse, asymmetrical theta. MRI showed in 4 cases caudate and lenticular hyperintensity and 2 diffuse cerebral atrophy.

LEV was administered at doses of 2000–3000 mg/daily with low titration. Treatment lasted 3–6 months. At present, only one patients is still alive; the survival of dead ones was 2–12 months.

Results: All patients showed during treatment, a marked reduction of myoclonus from moderate intense to mild form; some patients were myoclonus-free during part of the day.

Conclusions: Initially or during the course of CJD, approximately 90% of patients present movement disorders, especially generalised myoclonus. Many drugs have been used in the treatment, including prednisone, levodopa, haloperidol, benzodiazepines and anticonvulsants. On the basis of our results, we can recommend LEV as a safe and effective treatment of myoclonus in CJD.

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EVALUATION OF THE PHARMACOKINETIC INTERACTION OF BRIVARACETAM ON OTHER ANTIEPILEPTIC DRUGS IN ADULTS WITH PARTIAL-ONSET SEIZURES

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Rationale: To assess the effect of brivaracetam (BRV) adjunctive treatment on steady-state plasma concentrations of concomitant antiepileptic drugs (AEDs) in adult patients.

Methods: Patients with refractory epilepsy received oral BRV (5, 20, 50, or 150 mg/day) or placebo BID during 7 to 10 week in 2 double-blind, placebo-controlled, parallel-group, dose-ranging studies in adjunctive treatment of partial-onset seizures.

At baseline and during treatment with either add-on BRV or placebo, AED plasma concentrations (carbamazepine [CBZ] and its epoxide [CBZ-E], lamotrigine [LTG], levetiracetam [LEV], 10-hydroxy oxcarbazepine [OXC], phenytoin [PHT], topiramate [TPM] and valproate [VPA]) were determined during clinical visits. Data were analysed using repeated measures covariance analysis with baseline as covariate, following logarithmic transformation. Pharmacokinetic interaction was evaluated using the bioequivalence approach (90% confidence intervals [CI] of the geometric mean concentrations ratios relative to the baseline).

Results: Approximately 70% of 343 patients (51% female; age range 16–65 years), received BRV in addition to 1 or 2 concomitant AEDs (CBZ 41%, LTG 27%, VPA 19%, LEV 18%, OXC 15%, PHT 14%, TPM 13%). Mean plasma concentrations (CV = coefficient of variation) varied from baseline to BRV treatment period as follows: CBZ 8.8 to 8.5 μg/mL (CV = 40%), CBZ-E 1.8 to 2.5 μg/mL (CV = 53%), LEV 36.3 to 40.2 μg/mL (CV = 48%), LTG 5.8 to 6.2 μg/mL (CV = 81%), OXC 20.5 to 20.3 μg/mL (CV = 41%), PHT 8.6 to 10.7 μg/mL (CV = 75%), TPM 7.4 to 7.5 μg/mL (CV = 74%), VPA 73 to 72 μg/mL (CV = 45%). The geometric mean ratio of concentrations (BRV *vs.* baseline) was centered around 100% for CBZ, LEV, LTG, OXC, TPM and VPA and CI's were within the 80–125% limits of bioequivalence. No BRV dose-related trend was observed for these AEDs. For CBZ-E, a moderate increase was observed at the highest dose. The mean CBZ-E/CBZ ratio was 0.23, 0.24, 0.26, 0.29 and 0.38 for placebo and BRV 5, 20, 50 and 150 mg/day, respectively. Mean PHT plasma concentrations ratios over baseline were approximately 25% higher in patients receiving BRV 20 and 50 mg/day (no PHT patient at 150 mg/day) than in the placebo group, but there was no dose-related trend and numbers of patients were small (10 to 13 patients per dose).

Conclusions: BRV 5–150 mg/day did not appear to modify the steady-state plasma concentrations of concomitantly administered CBZ, LTG, LEV, OXC, TPM and VPA in adult patients with partial-onset seizures. CBZ-E was modestly increased at the highest dose. The potential effect on PHT was equivocal. Results suggest that no dose adjustment of any of these AEDs is required when BRV 5–150 mg/day is added to combination therapy.

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SINGLE- AND MULTIPLE-DOSE BIOEQUIVALENCE AND FOOD EFFECT COMPARISON BETWEEN LEVETIRACETAM EXTENDED RELEASE TABLETS ONCE DAILY AND LEVETIRACETAM IMMEDIATE RELEASE TABLETS TWICE DAILY IN HEALTHY SUBJECTS

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Rationale: To compare the bioavailability of a new extended release levetiracetam 500 mg tablet (LEV XR) given once daily (OD) with that of levetiracetam 500 mg immediate release tablet (LEV IR; Keppra®) given twice daily (BID); to assess the effect of food on LEV XR.

Methods: 24 healthy subjects (12M/12F) were randomised in this open-label, 3-way Latin square cross-over study. Under fasting conditions, 500 mg LEV IR BID or 2 x 500 mg LEV XR OD was administered on day 1 and from days 3 to 9. Plasma LEV concentration was determined serially on days 1 and 9. A single dose of 2 x 500 mg LEV XR was administered in the third treatment arm with a standard high-fat breakfast. Bioequivalence or lack of food effect was concluded if the 90% confidence intervals (CIs) of the pairwise adjusted geometric means ratios (XR/IR or fed/fasted) were entirely contained within 80–125% limits for C_{max}, $AUC_{(0-t)}$ and AUC, and for C_{max} and $AUC_{(0-24)}$ at steady-state.

Results: Under fasting conditions, the time to peak was delayed by approximately 3 h with LEV XR (4 h *vs.* 0.9 h). CIs for comparisons of C_{max}, $AUC_{(0-t)}$ and AUC ratios after single dosing were all within the bioequivalence limits. The steady-state $AUC_{(0-24)}$ ratios were also within the acceptance range. The average steady-state plasma concentration ($C_{ss,av}$)) was 12.9 μg/mL (13 CV%) and 13.6 μg/mL (16 CV%) for the XR and IR tablets, respectively. The time during which the LEV concentration remained ≥75% of C_{max} was 7.8 h (27 CV%) *vs.* 3.4 h (67 CV%). The peak-to-trough fluctuation ratio (PTF) was 1.19 (12 CV%) *vs.* 1.27 (22%). When LEV XR was taken with a high-fat meal, the time to peak was delayed, but the C_{max}) and AUC ratios remained within the bioequivalence limits. Drug-related adverse events (AEs), mostly of mild intensity, were reported by 13 (54%) and 17 (71%) subjects on LEV XR and LEV IR, respectively. The type and incidence of AEs following LEV XR did not differ from LEV's known tolerability profile. All AEs resolved at the end of the study.

Conclusions: The new LEV XR 500 mg tablet given OD is bioequivalent to the LEV IR tablet (Keppra®) given BID and its absorption is not modified by food intake.

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