Effect of Food on the Pharmacokinetic Profile of Eslicarbazepine Acetate (BIA 2-093)

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Abstract

Objective: To investigate the effect of food on the pharmacokinetics of eslicarbazepine acetate (BIA 2-093), a new voltage-gated sodium channel antagonist.

Material and methods: Single-centre, open-label, randomised, two-way crossover study in 12 healthy subjects. The study consisted of two consecutive treatment periods separated by a washout of 14 days or more. In each of the study periods subjects were administered a single dose of eslicarbazepine acetate 800mg following either a standard high-fat content meal or 10 hours of fasting.

Results: Eslicarbazepine acetate was rapidly and extensively metabolised to BIA 2-005. Maximum BIA 2-005 plasma concentrations (C_max) in fed (test) and fasting (reference) conditions were, respectively, 12.8 ± 1.8 µg/mL and 11.3 ± 1.9 µg/mL, and the areas under the plasma concentration time curve from 0 to infinity (AUC_∞) were, respectively, 242.5 ± 32.1 µg • h/mL and 243.6 ± 31.1 µg • h/mL (arithmetic mean ± SD). The point estimate (PE) and 90% confidence interval (90% CI) of the test/reference C_max geometric mean ratio were 1.14 and 1.04, 1.25, respectively; for the AUC_∞ ratio, the PE and 90% CI were 1.00 and 0.95, 1.04, respectively. Bioavailability of eslicarbazepine acetate administered in fed and fasting conditions was similar and bioequivalence is accepted for both AUC_∞ and C_max because the 90% CI lies within the acceptance range of 0.80, 1.25. No statistically significant differences were found in time of occurrence of C_max.

Conclusion: The presence of food had no significant effect on the pharmacokinetics of eslicarbazepine acetate and therefore this new voltage-gated sodium channel antagonist may be administered without regard to meals.

Eslicarbazepine acetate [BIA 2-093, S-(-)-10-acetoxy-10, 11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide] is a novel voltage-gated sodium channel antagonist that competitively interacts with site 2 of the inactivated state of the channel. Its affinity for the inactivated state of the channel is similar to that of carbamazepine, while the affinity for the resting state is about 3-fold lower than that of carbamazepine. This profile suggests a possible enhanced inhibitory selectivity of eslicarbazepine acetate for rapidly firing neurons over those displaying normal activity.

Eslicarbazepine acetate is chemically related to carbamazepine and oxcarbazepine, but has been
specifically designed to avoid the production of toxic metabolites (such as epoxides) and to overcome enantiomeric impurity and the unnecessary production of enantiomers or diastereoisomers of metabolites and conjugates, without losing anti-epileptic potency.\[2\]

Previous human studies in which a chiral method has been used in the assay of plasma drug concentrations showed that eslicarbazepine acetate is rapidly and extensively transformed into the active metabolite eslicarbazepine (also known as S-licarbazepine).\[3\] This metabolite represents >95% of systemic drug exposure following oral administration of eslicarbazepine acetate and it is the main metabolite responsible for the pharmacological activity of the drug. The plasma concentration of the parent drug has been systematically found to be below the limit of quantification of the assay (10 µg/L). When a non-chiral method is used, as was the case in the current study, the assay is not able to distinguish between eslicarbazepine and its R-enantiomer, a minor metabolite, and the mixture is reported as BIA 2-005.\[4,5\]

Entry-into-man studies in healthy subjects administered single oral doses of eslicarbazepine acetate ranging from 20mg to 1200mg\[4\] and multiple doses ranging from 200mg twice daily to 1200mg once daily\[5\] showed that the maximum observed plasma concentration ($C_{\text{max}}$) of BIA 2-005 was attained at 1–4 hours post-dose ($t_{\text{max}}$). These studies also showed that the extent of systemic exposure to BIA 2-005 was approximately dose-proportional, and that steady-state plasma concentrations were attained at 4–5 days, consistent with an effective half-life of 20–24 hours. Eslicarbazepine acetate was also shown to be effective and well tolerated in a therapeutic exploratory study in epileptic patients refractory to standard antiepileptic drug therapy,\[6\] and confirmatory therapeutic clinical trials are currently ongoing.

In the present work we describe the results of a study aiming to investigate the effect of food on the pharmacokinetics of a single oral dose of eslicarbazepine acetate 800mg in healthy subjects.

**Methods**

**Study Design**

This was an open-label, randomised, two-way crossover study performed at BIAL’s Human Pharmacology Unit (S. Mamede do Coronado, Portugal). The study consisted of two periods separated by a washout period of 14 days or more. In each of the study periods the volunteers randomly received a single oral dose of eslicarbazepine acetate 800mg after either a standard high-fat content breakfast or 10 hours of fasting. The randomised, balanced, single-dose, two-treatment (fed vs fasting), two-period, two-sequence crossover design is acceptable for studying the effects of food on drug bioavailability.\[7\]

For each treatment period, subjects were admitted to the unit approximately 24 hours prior to receiving the study medication and remained in the unit under clinical observation until at least 48 hours post-dose; they were then asked to leave and to return for the 72- and 96-hour post-dose procedures. Following administration of eslicarbazepine acetate (four tablets of 200mg strength each) in fasting or fed conditions, a standard lunch was provided approximately 4 hours post-dose, a snack at 8 hours post-dose, and a dinner 12 hours post-dose. Water *ad libitum* was allowed. The standard high-fat content meal consisted of two eggs scrambled in butter, two strips of bacon, two slices of buttered toasted white bread and corn flakes with 200mL of whole milk. The breakfast was eaten within 30 minutes and drug administration occurred immediately thereafter.

Tablets containing eslicarbazepine acetate were manufactured by BIAL (S. Mamede do Coronado, Portugal) in accordance with Good Manufacturing Practice.

The study was conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice (ICH) guidelines. An independent ethics committee (Comissão de Ética Independente da UFH, Porto, Portugal) reviewed and approved the study protocol and information for subjects. Written
Informed consent was obtained for each subject prior to enrolment in the study.

Subjects

Twelve healthy male volunteers aged 18–45 years with a body mass index of 19–28 kg/m² participated in the study. The sample size chosen (12 subjects completed and evaluable) is the minimum sample size required by current regulatory guidance and provided at least 80% power to detect a 20% difference in the area under the concentration versus time curve (AUC) and Cmax for BIA 2-005 in an equivalence range of 0.80–1.25 and α = 0.05. Participants’ health was assessed on the basis of medical history, physical examination, ECG, electroencephalogram and clinical laboratory safety tests (haematology, coagulation status, plasma biochemistry, urinalysis and hepatitis B, hepatitis C and HIV serology). Tests for use of drugs and alcohol were performed at screening and each admission. No concomitant medication was allowed during the study, except if required for treatment of adverse events. During participants’ stays at the Unit, a standard diet was served and alcohol, caffeine and grapefruit-containing food and beverages were prohibited.

Assessment Procedures

Complete medical history and physical examination were performed at screening and updated at each admission.

During each study period, blood pressure and heart rate measurements were obtained at frequent intervals (1, 2, 4, 8, 12, 24, 48, 72 and 96 hours post-dose). A brief neurological examination was performed pre-dose and at 3, 6, 24, 48 and 96 hours post-dose. Continuous lead-II ECG monitoring was performed 0–4 hours post-dose; 12-lead ECG recordings were obtained pre-dose and at 6, 24, 72 and 96 hours post-dose. Clinical laboratory tests (haematology, coagulation status, plasma biochemistry and urinalysis) were performed at admission and 96 hours post-dose during each study period. Additional and repeat testing could be performed at the discretion of the investigator.

A follow-up visit was conducted approximately 2 weeks after the last dose. At this point, the medical history and physical examination were updated, and 12-lead ECG and clinical laboratory safety tests performed.

All clinical adverse events were monitored throughout the entire study. Each adverse event was described in detail: onset time and date, offset time and date, description of occurrence, severity, relationship to investigational product, action taken and outcome.

During each treatment period, blood samples (10mL) for drug plasma assay were taken at the following times: pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 and 96 hours post-dose. Blood samples were drawn either by direct venipuncture or via an intravenous catheter into lithium heparin Vacutainer® tubes and centrifuged at approximately 1500g for 10 minutes at 4°C. The resulting plasma was to be separated into two equal aliquots of 2mL and stored at –20°C until required for analysis. Plasma drug concentrations were determined using isocratic liquid chromatography with single quadrupole mass spectrometric detection.

Analysis

Pharmacokinetic Analysis

The pharmacokinetic parameters were derived by non-compartmental analysis using WinNonlin Version 4.0 (Pharsight Inc., Mountain View, CA, USA). The following parameters for BIA 2-005 were derived, where appropriate, from the individual plasma concentration-time profile: Cmax; the time of occurrence of Cmax (tmax); the AUC from time zero to the last sampling time at which the drug concentration was at or above the limit of quantification (10 μg/L) [AUCt], calculated by the linear trapezoidal rule; the AUC from time zero to infinity, calculated from AUCt + (Clast/λz), where Clast is the last quantifiable drug concentration (AUC∞); the apparent terminal rate constant, calculated by log-linear regression of the terminal segment of the plasma concentration versus time curve (λz); and the apparent terminal half-life (t½z), calculated from ln 2/λz.

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Actual sampling times were used for the pharmacokinetic analysis. Special consideration was given to the estimation of $\lambda_z$ and corresponding $t_{1/2}$ values. Values for $\lambda_z$ were calculated from a minimum of three data-points. The $\lambda_z$ values determined from three data-points and the values calculated over a period that were less than 2-fold greater than the corresponding $t_{1/2}$ were noted in the appropriate tables. Where an AUC was extrapolated to infinity, the percentage of the extrapolated area to the total area was assessed, and if >20%, the AUC value was flagged as unreliable. Plasma concentrations below the limit of quantification of the assay were taken as zero for all calculations. Summary statistics of all data for each treatment and schedule sampling time were reported, as appropriate, using the geometric mean, arithmetic mean, standard deviation (SD), coefficient of variation (CV), median, minimum and maximum values.

The effect of food on the pharmacokinetics of eslicarbazepine acetate was studied in accordance with the statistical method for testing relative bioavailability (e.g. bioequivalence) in which the 90% confidence interval (90% CI) for the geometric mean ratio (point estimate [PE]) of the observed pharmacokinetic parameters with (fed = test) and without (fasting = reference) food should be reported. For this purpose, $AUC_\infty$ and $C_{\text{max}}$ of BIA 2-005 were compared using analysis of variance (ANOVA). PEs and two one-sided 90% CIs for the ratios were calculated by re-transformation of the logarithmic data using the intra-individual SD of the ANOVA.[8] The 90% CI for the parameters under consideration should lie within the acceptance interval of 0.80, 1.25.[7-9] Although statistical evaluation of $t_{\text{max}}$ is relevant only if there is a clinically relevant claim for rapid release or action or signs related to adverse effects, which presumably is not the case for eslicarbazepine acetate, a $t_{\text{max}}$ comparison between the fasting and fed conditions was performed assuming a non-parametric approach using the Wilcoxon signed rank test (untransformed values).

The statistical package SAS version 8.2 (SAS Institute, Cary, NC, USA) was used in all computations.

**Results**

**Population**

A total of 12 male subjects were enrolled in and completed the study. Their mean ± SD demographic data were: age 26.2 ± 6.6 (range 20–45) years; height 179 ± 8 (166–196) cm; weight 73.7 ± 8.0 kg.

**Tolerability**

Individual and summarised blood pressure, heart rate, neurological examination and clinical laboratory data were presented in tabular form with mean, median, SD and range (minimum and maximum) values as appropriate. For the laboratory safety data, out-of-range values were flagged in the data listings and a list of clinically significantly abnormal values was presented. Adverse events were tabulated and summarised according to the Medical Dictionary for Regulatory Activities (MedDRA, version 4.0).
Effect of Food on Pharmacokinetics of Eslicarbazepine Acetate

Table I. Pharmacokinetic parameters of BIA 2-005 following oral administration of eslicarbazepine acetate 800mg in fasting and fed conditions (n = 12)∗

<table>
<thead>
<tr>
<th>Condition</th>
<th>$C_{\text{max}}$ (µg/mL)</th>
<th>$t_{\text{max}}$ (h)</th>
<th>$AUC_t$ (µg • h/mL)</th>
<th>$AUC_{\infty}$ (µg • h/mL)</th>
<th>$\lambda_z$ (1/h)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>11.3 (1.9)</td>
<td>3.5 (0.5–8.0)</td>
<td>243.2 (31.2)</td>
<td>243.6 (31.1)</td>
<td>0.0780 (0.00814)</td>
<td>8.98 (0.992)</td>
</tr>
<tr>
<td>Fed</td>
<td>12.8 (1.8)</td>
<td>4.0 (0.5–8.0)</td>
<td>229.4 (41.4)</td>
<td>242.5 (32.1)</td>
<td>0.0721 (0.0107)</td>
<td>9.83 (1.62)</td>
</tr>
</tbody>
</table>

a Results are expressed as arithmetic means with standard deviations in parentheses unless otherwise specified.

$\lambda_z$ = apparent terminal rate constant calculated by log-linear regression of the terminal segment of the plasma concentration vs time curve;

$AUC_{\infty}$ = area under the plasma concentration time curve from 0 to infinity; $AUC_t$ = the area under the plasma concentration-time curve from time zero to the last sampling time at which the drug concentration was at or above the limit of quantification; $C_{\text{max}}$ = maximum plasma concentration; $t_{1/2}$ = apparent terminal half-life; $t_{\text{max}}$ = time to reach $C_{\text{max}}$.

(60.1–93.0) kg, and body mass index 23.1 ± 2.0 (20.5–27.0) kg/m². Ten subjects (83.3%) were students and two were professionally active (16.7%). Eleven subjects (91.7%) were Caucasian and one subject (8.3%) was of mixed race.

Pharmacokinetic Analysis

Mean plasma BIA 2-005 concentration-time profiles and pharmacokinetic parameters obtained following a single oral dose of eslicarbazepine acetate 800mg in fasting and fed conditions are summarised in figure 1 and table I.

$C_{\text{max}}$ for BIA 2-005 was reached ($t_{\text{max}}$) between 0.5 and 8.0 hours post-dose (median 3.5 hours) in fasting conditions, after which concentrations declined with an approximate mean apparent terminal $t_{1/2}$ of 9.0 hours (7.9–10.8 hours). Following the standard meal, $C_{\text{max}}$ for BIA 2-005 was reached ($t_{\text{max}}$) between 0.5 and 8.0 hours post-dose (median 4.0 hours), with $t_{1/2}$ of 9.8 hours (8.0–13.1 hours).

The geometric means (±SD) of $C_{\text{max}}$ and $AUC_{\infty}$ were, respectively, 11.2 (±1.9) µg/mL and 241.7 (±31.1) µg • h/mL in fasting conditions, and 12.7 (±1.8) µg/mL and 240.6 (±32.1) µg • h/mL in fed conditions. Table II depicts the PEs and 90% CIs of the pharmacokinetic parameters obtained after administration of eslicarbazepine acetate following a standard meal over those obtained following administration in fasting conditions. The extent of formation of BIA 2-005, as reflected by the $C_{\text{max}}$ values, also fits the claim of bioequivalence between the two administrations, with a PE of 1.14 and a 90% CI of 1.04, 1.25.

No statistical differences were found between $t_{\text{max}}$ values for BIA 2-005 following administration of eslicarbazepine acetate in fasting and fed conditions.

Tolerability

During the course of the study, 20 adverse events were reported in total. One adverse event (a vasovagal reaction during venipuncture) occurred pre-treatment, and, therefore, 19 treatment-emergent adverse events were reported by ten subjects. Of these, 12 adverse events, reported by eight subjects, were considered to be possibly related to treatment. All treatment-emergent adverse events were mild in severity except one case of venipuncture-related paraesthesia (reported as unrelated to treatment). The incidence of adverse events was similar when eslicarbazepine acetate was administered in fasting or fed conditions. There were no serious adverse events, deaths or discontinuations due to adverse

Table II. Point estimates (PES) and 90% confidence intervals (90% CIs) for the comparison of maximum plasma concentration ($C_{\text{max}}$) and area under the plasma concentration time curve from 0 to infinity ($AUC_{\infty}$) of BIA 2-005 following oral administration of eslicarbazepine acetate 800mg in fed and fasting conditions

<table>
<thead>
<tr>
<th>BIA 2-005</th>
<th>Fed/fasting</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ PE</td>
<td>1.14</td>
</tr>
<tr>
<td>90% CI</td>
<td>1.04, 1.25</td>
</tr>
<tr>
<td>$AUC_{\infty}$ PE</td>
<td>1.00</td>
</tr>
<tr>
<td>90% CI</td>
<td>0.95, 1.04</td>
</tr>
</tbody>
</table>
events. No clinically relevant abnormalities were observed in blood pressure, heart rate, clinical laboratory safety tests or ECG parameters during the study.

**Discussion**

The primary objective of this study was to investigate the effect of food on the pharmacokinetics of eslicarbazepine acetate. Eslicarbazepine acetate appeared to be rapidly metabolised to BIA 2-005, which is in agreement with the results of other studies.\(^1\)\(^{-}^{4,5}\)

AUC\(_{\infty}\) and C\(_{\text{max}}\) of BIA 2-005 were defined as the main parameters for the assessment of bioavailability and bioequivalence of eslicarbazepine acetate administered in fasting and fed conditions, which is in agreement with current regulatory guidelines.\(^7\)\(^{-}^{9,10}\) The fed/fasting geometric mean ratios for AUC\(_{\infty}\) and C\(_{\text{max}}\) were associated with PEs of 1.00 (90% CI 0.95, 1.04) and 1.14 (90% CI 1.04, 1.25), respectively. For both of the BIA 2-005 pharmacokinetic parameters assessed (AUC\(_{\infty}\) and C\(_{\text{max}}\)), the 90% CIs were contained within the 0.80, 1.25 acceptance interval.\(^7\)\(^{-}^{9,10}\) Therefore, it can be concluded that systemic exposure to the active metabolite was essentially similar following administration of eslicarbazepine acetate in fasting and fed conditions. The clinical consequence of this finding is that eslicarbazepine acetate may be administered to patients without regard to meals.

**Conclusion**

This study showed that the presence of food has no significant effect on the pharmacokinetics of eslicarbazepine acetate and therefore this new voltage-gated sodium channel antagonist can be administered without regard to meals.

**Acknowledgements**

This work was financially supported by BIAL S.A.

**References**


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