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Single-Dose and Steady-State Pharmacokinetics of Eslicarbazepine Acetate (BIA 2-093) in Healthy Elderly and Young Subjects

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Eslicarbazepine acetate (BIA 2-093, S(-)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide) is a new drug currently in phase III for the treatment of epilepsy and phase II for bipolar disorder. It 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 pharmacological activity. Eslicarbazepine acetate is a voltage-gated sodium channel blocker that competitively interacts with site 2 of the inactivated state of the channel. The affinity for this state of the channel is similar to that of carbamazepine, while the affinity for the resting state of the channel is about 3-fold lower than that of carbamazepine. This profile may suggest an enhanced inhibitory selectivity of eslicarbazepine acetate for rapidly firing neurons over those displaying normal activity.

Studies in humans have shown that after oral administration, eslicarbazepine acetate is rapidly and extensively metabolized to the active metabolite eslicarbazepine, the S(+) enantiomer of licarbazepine (S-licarbazepine, (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide). The plasma concentrations of the parent drug (eslicarbazepine acetate) have been systematically found below the limit of quantification of the assay (10 ng/mL). When a nonchiral method is used, the assay does not distinguish between eslicarbazepine and its R-enantiomer, a minor metabolite, and the mixture is reported as BIA 2-005.

Entry-into-man studies in healthy subjects administered eslicarbazepine acetate single oral doses ranging from 20 mg to 1200 mg and multiple doses ranging from 200 mg twice daily to 1200 mg once daily showed that BIA 2-005 maximum observed plasma concentration (Cmax) was attained at 1 to 4 hours postdose (tmax), the extent of systemic exposure to BIA 2-005 was approximately dose proportional, and steady state of BIA 2-005 plasma concentrations was attained at 4 to 5 days, consistent with an effective half-life of 20 to 24 hours. The mean renal clearance of BIA 2-005 from plasma was 20 to 30 mL/min, and the total amount of BIA 2-005 recovered in the urine was approximately 20% and 40% within 12 hours and 24 hours postdose, respectively. In a placebo-controlled therapeutic exploratory study in epileptic patients refractory to standard antiepileptic drug therapy, eslicarbazepine acetate in daily doses ranging from 400 mg to 1200 mg administered in a once-daily or twice-daily regimen was shown to be effective and well-tolerated.

Treatment of elderly patients often requires information on whether dose adjustments are needed. Most of the recognized important differences between younger and older patients are pharmacokinetic differences, often related to impairment of excretory function or to
drug-drug interactions. The primary objective of this study was to answer that question by comparing the pharmacokinetic profile of eslicarbazepine acetate in young and elderly subjects.

**METHODS**

**Study Design**

This was a single-center, open-label, nonrandomized study performed at Scope International Life Sciences AG (Hamburg, Germany) in 12 healthy elderly and 12 healthy young subjects. The study consisted of a single-dose phase (phase A) followed by a 8-day multiple-dose phase (phase B). Subjects were administered eslicarbazepine acetate 600 mg single dose in phase A and 600 mg once daily in phase B.

In phase A, subjects were admitted to the unit on the day before dosing (day 0) and remained under clinical supervision until at least 24 hours postdose (day 2); then, they left and were requested to attend the unit at 36, 48, 72, and 96 hours postdose. Phase B started following the 96-hour postdose procedures of phase A (day 5). On days 5 to 11, subjects were requested to attend the unit early in the morning for predose blood sampling for the assay of trough plasma concentrations and study product administration. On the evening of day 11, subjects were admitted to the unit, and on the morning of day 12, the last dose of study medication was administered. Subjects remained under clinical supervision until the 24-hour postdose procedures (day 13); then, they left and were requested to attend the unit in the evening of day 13 and in the morning of days 14, 15, 16, and 17 for the 36-, 48-, 72-, 96-, and 120-hour post–last dose procedures, respectively.

The study was conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice recommendations, and an Independent Ethics Committee (Ethik-Kommission der Ärztekammer Hamburg, Hamburg, Germany) reviewed and approved the study protocol and the subject information. Written informed consent was obtained for each subject prior to enrolment in the study.

**Subjects**

Subjects satisfied the following main inclusion criteria: aged between 18 and 40 years (young group) or 65 years or older (elderly group); within 15% (if young) or 20% (if elderly) of ideal body weight; “healthy” as determined by prestudy medical history, physical examination, neurological examination, 12-lead electrocardiogram, and clinical laboratory tests; nonsmokers or smokers of less than 10 cigarettes per day; if female, not of childbearing potential or, if of childbearing potential, using double-barrier or intrauterine device methods and having a negative pregnancy test.

Eslicarbazepine acetate administration occurred between 8:00 AM and 9:00 AM following an overnight fasting of at least 8 hours on day 1 (single dose of phase A) and day 12 (last dose of phase B). On days 5 to 11, dosing occurred without regard to meals because a previous food-interaction study showed that presence of food has no effect on the pharmacokinetics of eslicarbazepine acetate. On days 1 and 12, meals were served about 4, 7, and 11 hours following product administration. Water drinking as desired was allowed.

**Blood Sampling**

Blood samples (7 mL) for drug plasma assays were taken at the following times: phase A: predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours postdose; phase B: from day 5 to day 11 inclusive, before the daily dose (for trough concentration assay); day 12: predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours postdose. Blood samples were drawn into lithium heparin tubes and centrifuged at approximately 1500 g for 10 minutes at 4°C. The resulting plasma was separated into 2 equal aliquots of 1 mL and stored at −20°C until required for analysis.

**Sample Analysis**

Eslicarbazepine acetate, eslicarbazepine, and R-licarbazepine concentrations in plasma were analyzed using validated isocratic liquid chromatography with single quadrupole mass spectrometric detection (MS). The MS detector was operated in positive ion mode with mass transitions for eslicarbazepine acetate, eslicarbazepine, R-licarbazepine, and the internal standard (10,11-dihydrocarbamazepine) of 319.16 amu (200 ms), 277.08 amu (200 ms), 277.08 amu (200 ms), and 261.05 amu (200 ms), respectively. The overall imprecision of the method, measured by the coefficient of variation, ranged from 6.7% to 7.4% for eslicarbazepine acetate, from 6.7% to 9.6% for eslicarbazepine, and from 7.8% to 9.4% for R-licarbazepine. The mean accuracy ranged from 98.8% to 99.0% for eslicarbazepine acetate, from 98.1% to 102.8% for eslicarbazepine, and from 96.9% to 98.8% for R-licarbazepine. The limit of quantification of the assay was 50 ng/mL for eslicarbazepine acetate and 100 ng/mL for eslicarbazepine and R-licarbazepine.
Pharmacokinetic Analysis

The following pharmacokinetic parameters were calculated by the standard method for noncompartmental analysis using the WinNonlin program (version 4.0; Pharsight Corporation, Mountain View, Calif): peak plasma concentration (C\text{max}); time to reach C\text{max} (t\text{max}); area under the plasma concentration-time curve (AUC) from time 0 to the last quantifiable concentration (AUC\text{last}), calculated by the linear trapezoidal method; AUC over the dosing interval (AUC\text{0-24}); AUC from time 0 to infinity (AUC\text{0-}\infty), calculated from AUC\text{0-t} + (C\text{last}/\lambda\text{z}), where C\text{last} is the last quantifiable concentration; apparent terminal rate constant (\lambda\text{z}) calculated by log-linear regression of the terminal segment of the plasma concentration-time profile; apparent terminal elimination half-life (t\text{1/2}), calculated from ln 2/\lambda\text{z}; and observed degree of accumulation (R\text{0}) calculated from AUC\text{0-}\infty(day 12)/AUC\text{0-}\infty(day 1).

Comparisons between age groups were performed by 1-way analysis of variance of the logarithmic transformed parameters (C\text{max}, AUC\text{0-24}, and AUC\text{0-}\infty). Point estimates and 95% confidence intervals (95% CIs) were calculated for the elderly/young ratio of these pharmacokinetic parameters for single and multiple dose. The statistical package SAS (version 8.2; SAS Institute Inc, Cary, NC) was used.

RESULTS

Subjects

Twelve young subjects (6 males and 6 females; mean ± SD age = 29.8 ± 7.03 years, range = 18-38 years; height 175 ± 9 cm, range = 158-186 cm; weight 70.1 ± 13.3 kg, range = 48-98 kg) and 12 elderly subjects (6 males and 6 females; mean ± SD age = 69.9 ± 5.38 years, range = 65-80 years; height 171 ± 11 cm, range = 149-187 cm; weight 76.8 ± 13.1 kg, range = 55-104 kg) completed the study according to the protocol and were available for pharmacokinetic analysis. All subjects were Caucasian.

Pharmacokinetic Results

Plasma concentrations of parent drug (eslicarbazepine acetate) were systematically found to be below the limit of quantification, and therefore the concentration-time profiles and pharmacokinetic parameters could not be determined. Figure 1 displays the mean eslicarbazepine and R-licarbazepine concentration-time profiles following a 600-mg single dose (phase A), mean predose (trough) values during administration of
600 mg once daily for 8 days (phase B), and mean concentration-time profiles following the last dose of phase B.

The arithmetic mean ± SD of the main eslicarbazepine pharmacokinetic parameters in the young and elderly groups following a 600-mg single dose (phase A) and the last dose of phase B are presented in Table I. Eslicarbazepine was shown to be the major metabolite, representing approximately 97% and 98% of total systemic exposure (as assessed by AUC0-24) following a 600-mg single dose of eslicarbazepine in elderly and young subjects, respectively. Following multiple administration, the steady state of eslicarbazepine plasma concentrations was attained at 4 to 5 days of administration in both age groups, consistent with an effective half-life on the order of 17.8 hours (young group) and 16.8 hours (elderly group), calculated from the theoretical degree of accumulation (R0), where λz is the key value for its determination (t1/2eff. = ln 2 / λz) in accordance with Boxenbaum and Battle.8 In the young and elderly groups, an observed accumulation factor (R0) of, respectively, 1.64 and 1.59 was estimated. Following multiple administration of eslicarbazepine acetate for 8 days, eslicarbazepine was shown to represent approximately 95% and 96% of total systemic drug exposure in elderly and young subjects, respectively.

In phase A, the geometric means of Cmax, AUC0-24, and AUC0-∞ were, respectively, 9743 ng/mL, 135 253 ng•h/mL, and 177 298 ng•h/mL in the young group and 9232 ng/mL, 137 313 ng•h/mL, and 187 793 ng•h/mL in the elderly group. Following repeated administration (phase B), the geometric means of those pharmacokinetic parameters were, respectively, 16990 ng/mL, 209 997 ng•h/mL, and 289 233 ng•h/mL in the young group and 14 942 ng/mL, 206 628 ng•h/mL, and 291 723 ng•h/mL in the elderly group. The corresponding point estimates and 95% CIs were calculated and are included in Table I. No statistically significant difference appeared in any pharmacokinetic parameter, following single or repeated administration of eslicarbazepine acetate.

The difference in eslicarbazepine tmax between the elderly and young groups was –0.0417 hours (95% CI, –1.68, 1.60) following a single dose and 0.000 hours (95% CI, –1.07, 1.07) following repeated administration. No statistical differences were found between age groups.

DISCUSSION AND CONCLUSIONS

The primary objective of the study was to investigate the effect of age on the pharmacokinetics of eslicarbazepine acetate in young (18-40 years) and elderly (65 years or older) subjects. Eslicarbazepine acetate was shown to be extensively metabolized to eslicarbazepine (S-eslicarbazepine) and, in a minor extent, to R-eslicarbazepine. Eslicarbazepine represented between 95% and 98% of total systemic drug exposure (as assessed by AUC0-24; ie, AUC over the dosing interval) and therefore is expected to be mainly responsible for pharmacological activity following administration of eslicarbazepine acetate. With multiple dosing, steady-state plasma concentrations were attained at 4 to 5 days of administration in both age groups, consistent with an effective half-life on the order of 17 to 18 hours.

The kinetic profile of eslicarbazepine was similar in young and elderly subjects, and no statistical differ-
ences were found for any of the pharmacokinetic parameters assessed (Cmax, tmax, AUC0-24, and AUC0-∞) following both single and repeated administration of eslicarbazepine acetate. In this regard, the pharmacokinetic behavior of eslicarbazepine acetate is different from that of oxcarbazepine, in which an age-related difference in systemic exposure was reported.9 Oxcarbazepine is rapidly and extensively metabolized to a mixture of the S- and R-licarbazepine,10 both appearing in plasma and urine in the proportion of approximately 4:1.11-13 Substantial differences in the disposition of oxcarbazepine between young and elderly volunteers were found both for Cmax and AUC parameters. Cmax and AUC of the mixture of the S- and R-licarbazepine, the active metabolite of oxcarbazepine (also known as MHD), were 30% to 60% higher in elderly subjects (60-82 years of age) than in younger subjects (18-32 years of age). Differences were judged to be presumably due to age-related reductions in creatinine clearance and slower plasma elimination of MHD.14 It remains to be determined whether R-licarbazepine has a major role in the negative impact of oxcarbazepine pharmacokinetic profile in elderly subjects.

In conclusion, the pharmacokinetics of eslicarbazepine acetate was essentially similar in young and elderly subjects.

REFERENCES


