Steady-State Carbamazepine Pharmacokinetics Following Oral and Stable-Labeled Intravenous Administration in Epilepsy Patients: Effects of Race and Sex

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Carbamazepine is a widely prescribed antiepileptic drug. Owing to the lack of an intravenous formulation, its absolute bioavailability, absolute clearance, and half-life in patients at steady state have not been determined. We developed an intravenous, stable-labeled (SL) formulation in order to characterize carbamazepine pharmacokinetics in patients. Ninety-two patients received a 100-mg infusion of SL-carbamazepine as part of their morning dose. Blood samples were collected up to 96 hours after drug administration. Plasma drug concentrations were measured with liquid chromatography–mass spectrometry, and concentration–time data were analyzed using a noncompartmental approach. Absolute clearance (l/hr/kg) was significantly lower in men (0.039 ± 0.017) than in women (0.049 ± 0.018; $P = 0.007$) and in African Americans (0.039 ± 0.017) when compared with Caucasians (0.048 ± 0.018; $P = 0.019$). Half-life was significantly longer in men than in women as well as in African Americans as compared with Caucasians. The absolute bioavailability was 0.78. Sex and racial differences in clearance may contribute to variable dosing requirements and clinical response.

Carbamazepine (CBZ), a commonly prescribed antiepileptic drug, is a first-line treatment for partial seizures and is indicated for treatment of bipolar disorder and trigeminal neuralgia. Its use, however, is often limited by its complex pharmacokinetics, interactions with other drugs, and adverse effects.[1,2] CBZ is absorbed at a slow rate,[3–6] is moderately protein bound (65–85% to a combination of albumin and α-1-acid glycoprotein), and exhibits an initial low clearance rate that increases two- to threefold due to autoinduction.[4,7,8] CBZ also has an active metabolite, CBZ-10,11-epoxide (CBZ-E)[9,10] that possesses anticonvulsant activity and central nervous system toxicity similar to those of the parent compound.[11,12] CBZ metabolism takes place mainly through CYP3A4[13,14] and, to a lesser degree, through CYP3A5.[15]

The side effects of CBZ, including hyponatremia, cardiac conduction abnormalities, ataxia, nystagmus, and cognitive impairment, may be due, in part, to its narrow therapeutic range, the presence of CBZ-E, and CBZ's potential to interact with other drugs.[1,16] Because an intravenous formulation was not available in previous studies, detailed information was lacking on the pharmacokinetics of CBZ in patients on maintenance therapy, especially within the therapeutic dosage range (4–12 μg/ml). There is a need for rational dosing and monitoring strategies, developed from research in patients under steady-state conditions. Such strategies would lead to better management of therapy by reducing the incidence of CBZ-related adverse reactions, minimizing their severity, and improving seizure control. Simultaneous administration of intravenous and oral CBZ offers the best approach to attain this much-needed pharmacokinetic information.

Pairing the orally administered drug with intravenously administered, stable-labeled (nonradioactive) isotopes of the same compound, followed by mass spectrometry analysis constitutes a valuable tool for pharmacokinetic and bioavailability studies.[17] This method involves replacing a portion of the patient's usual oral dose with a coadministered intravenous stable isotope of the same drug. This approach permits measurement of the absolute bioavailability, absolute clearance, distribution volume, and elimination half-life—parameters that cannot usually be determined from oral dosing studies. For antiepilepsy drugs, it is the only method to achieve a

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rigorous characterization of the pharmacokinetics of the drug in patients under steady-state conditions. This is because interruption of drug therapy would expose the individual to an increased risk of seizures and is therefore contraindicated. Non-steady-state studies and those relying exclusively on data measured after oral administration of a drug have limitations because they do not fully characterize the pharmacokinetics of the drug under clinically relevant conditions. Injectable stable-isotope formulations have been successfully used by our group and others to determine phenytoin pharmacokinetics.[18–21] The objective of this study was to investigate the pharmacokinetics of intravenous CBZ and the effect of sex and race on CBZ disposition during steady-state conditions.

RESULTS

Data from 92 subjects were included in the pharmacokinetic analyses. The patient demographic information is shown in Table 1. The daily CBZ dose range (200–2,400 mg/day) reflects the dosage in normal clinical use.[22] All the subjects included in the analysis cohort completed the study protocol.

Table 1 Summary of patient characteristics

Characteristic	Value
N	92
Males/females	45/47
Age (years)	41 (11)
Weight (kg)	80.4 (20.1)
Daily CBZ dose (mg)	819 (514)
Race (AA/As/CA)	37/1/54
CBZ formulation: immediate/extended release	31/61

Values are presented as mean (standard deviation).

AA, African-American; As, Asian; CA, Caucasian; CBZ, carbamazepine.

The liquid chromatography–mass spectrometry assay readily distinguished intravenously administered SL-CBZ from non-labeled, orally administered immediate- and extended-release CBZ, as is shown in Figure 1a and 1b, respectively. The representative plot of data from a specific subject also illustrates the log-linear decline of SL-CBZ while the unlabeled CBZ concentrations remained relatively constant; this feature was a characteristic of all the subjects' concentration–time data.

A summary of CBZ pharmacokinetics is presented in Table 2. The values of both clearance and clearance adjusted for weight (Cl) were highly variable, ranging from 0.871 to 7.345 l/h and 0.010 to 0.095 l/h/kg, respectively. The mean Cl in men was lower than that in women (0.039 ± 0.017 l/h/kg vs. 0.049 ± 0.018 l/h/kg; $P = .007$). Similarly, Cl was lower in African Americans than in Caucasians (0.039 ± 0.017 l/h/kg vs. 0.048 ± 0.018 l/h/kg; $P = .019$). There was no interaction between the variables sex and race (Figure 2). On average, Caucasian women had a 67% greater weight-adjusted clearance than African-American men. Multiple-regression analysis revealed that sex and race accounted for 21.7% of the variance in Cl.

Half-life

The half-life of CBZ varied substantially, with the highest value being almost sevenfold greater than the lowest (range: 7.8–53.4 h). The mean half-life of CBZ in men was greater than that in women (22.7 ± 8.7 h vs. 17.5 ± 8.0 h; $P = .002$). The half-life

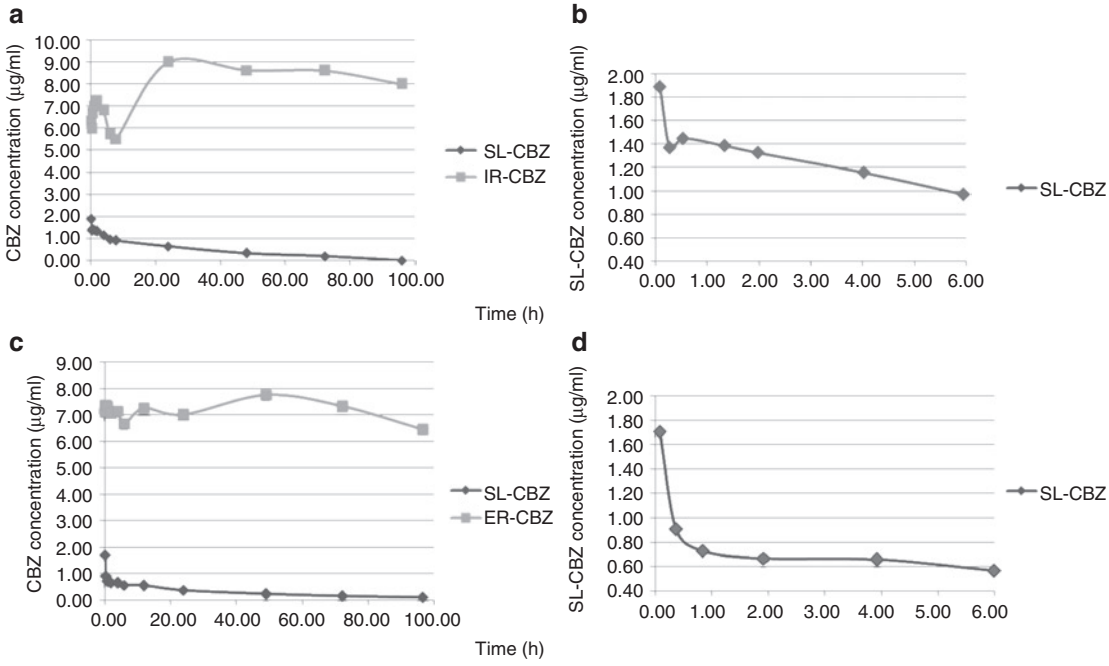

Figure 1 (**a**) A representative concentration–time curve for oral, immediate-release carbamazepine (IR-CBZ) and stable-labeled carbamazepine (SL-CBZ) administered intravenously to a male subject on 400 mg/day (b.i.d) of oral generic carbamazepine; volume of distribution = 1.0 l/kg; elimination half-life = 26.2 h. (**b**) Enlargement of the graph showing SL concentration from the immediate-release formulation. (**c**) A representative concentration–time curve for oral, extended-release carbamazepine (ER-CBZ) and SL-CBZ administered intravenously to a male subject on 600 mg/day (b.i.d.) Tegretol XR; volume of distribution = 1.1 l/kg; elimination half-life = 35.1 h. (**d**) Enlargement of the graph showing SL concentration from the extended-release formulation.

Table 2 Summary of carbamazepine pharmacokinetic parameters

	Total	Male	Female	AA	CA
	N = 92	*n* = 45	*n* = 47	*n* = 37	*n* = 54
Age	41 (11)	43 (11)	39 (11)	41 (11)	42 (12)
Weight (kg)	80.4 (20.1)	88.8 (17.2)	72.4 (19.5)	80.5 (21.4)	80.6 (19.5)
Dose/kg (mg)	10.4 (6.1)	9.7 (5.5)	10.9 (6.6)	9.9 (6.6)	10.6 (6.1)
C_{max} (SL); (μg/ml)	1.99 (0.80)	1.96 (0.87)	2.02 (0.73)	2.03 (0.86)	1.97 (0.77)
Half-life (h)	20.0 (8.7)	22.7 (8.7)*	17.5 (8.0)	22.4 (8.1)**	18.4 (8.8)
Clearance (l/h)	3.39 (1.22)	3.44 (1.41)	3.34 (1.02)	2.94 (1.02)	3.69 (1.27)
Cl (L/h/kg)	0.044 (0.018)	0.039 (0.017)***	0.049 (0.018)	0.039 (0.017)****	0.048 (0.018)
V_d (l)	89.78 (32.5)	102.19 (33.62)	77.90 (26.65)	90.17 (32.01)	90.68 (34.01)
V_d/kg (l/kg)	1.11 (0.26)	1.15 (0.31)	1.07 (0.20)	1.12 (0.28)	1.11 (0.25)
Bioavailability[a]	0.78 (0.24) *N* = 42	0.78 (0.23) *N* = 20	0.78 (0.25) *N* = 22	0.78 (0.25) *N* = 15	0.78 (0.24) *N* = 26
Carbamazepine Cp0 (μg/ml)	7.84 (3.11)	8.14 (3.15)	7.57 (3.07)	7.62 (2.92)	7.99 (3.24)
Carbamazepine-E Cp0 (μg/ml)	1.23 (0.79)	1.23 (0.78)	1.23 (0.80)	1.13 (0.71)	1.29 (0.84)
Fμ (free fraction)	0.26 (0.06) *N* = 72	0.26 (0.06) *N* = 36	0.25 (0.05) *N* = 36	0.25 (0.07) *N* = 35	0.26 (0.05) *N* = 37

AA, African-American; CA, Caucasian; Cl, clearance adjusted for weight; C_{max}, maximum concentration; Cp0, trough concentration; V_d, volume of distribution.

Values are reported as mean (standard deviation). [a]Bioavailability (*F*) was computed only on those subjects with a dosing interval of every 8 or every 12 h.

*P = .002. **P = .029. ***P = .007. ****P = .019.

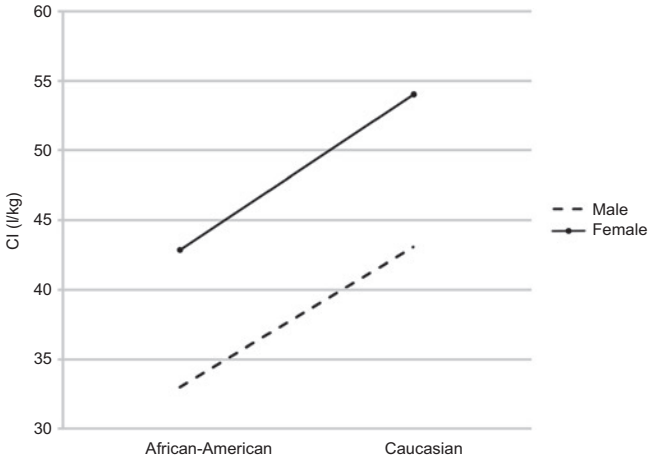

Figure 2 Comparisons of mean weight-adjusted clearance by sex and race.

in African Americans was also longer than that in Caucasians (22.4 ± 8.1 h vs. 18.4 ± 8.8 h; P = .029). In 26% of the subjects, the half-life was ≥ 24 h. As with Cl, there was no interaction between the variables sex and race with respect to CBZ half-life.

Bioavailability

The absolute bioavailability (*F*) was determined in a subset of 42 subjects (12 on immediate-release CBZ and 30 on extended-release CBZ). The mean and median fractions absorbed were 0.78 and 0.75, respectively, with substantial variability across subjects: the highest value was almost fourfold greater than the lowest value (range: 0.38–1.44) (**Figure 3**). There was no systematic difference in *F* by sex, race, or formulation of drug. In the 12 subjects taking immediate-release CBZ, the mean value of *F* was 0.80 ± 0.29 (range: 0.38–1.31) whereas the 30 subjects on extended-release CBZ had a mean *F* value of 0.78 ± 0.22 (range: 0.51–1.44). Moreover, there was no systematic difference among the patient groups with respect to daily oral dose (mg/kg), trough CBZ and CBZ-E concentrations, and volume of distribution.

DISCUSSION

This report provides new information on CBZ disposition in patients taking the medication under steady-state conditions. We found previously unreported sex- and race-related differences in Cl, elimination half lives exceeding 24 h, and high variability in absorption.

Although the women in our study exhibited greater CBZ Cl values than the men, the influence of sex on the clearance of drugs metabolized through the CYP3A pathway remains open to question.[23] However, our data, which represent drug metabolism observations isolated from the effects of absorption and active efflux/influx transport in the gut, are consistent with earlier observations that CYP3A substrates are eliminated more rapidly in women than in men.[24–27] The mechanism for the greater CYP3A activity is incompletely understood, and our study was not designed to elucidate the underlying processes. The sex-related difference in Cl is 25% on average, indicating that women require a larger CBZ dose on a mg/kg basis than do men.[28,29] In clinical practice, CBZ therapy is usually prescribed as fixed doses, and therefore the generally lower body weight in women compensates for the greater clearance. However, some women may require unusually large doses to attain the same plasma CBZ concentrations as men of comparable weight.

Before we began our study, several reports had been published describing polymorphisms in the gene encoding CYP3A5.[30] There has also been speculation about the roles of other CYP3A isoforms in producing the wide variability in the pharmacokinetic parameters of many CYP3A substrates.[31] Furthermore,

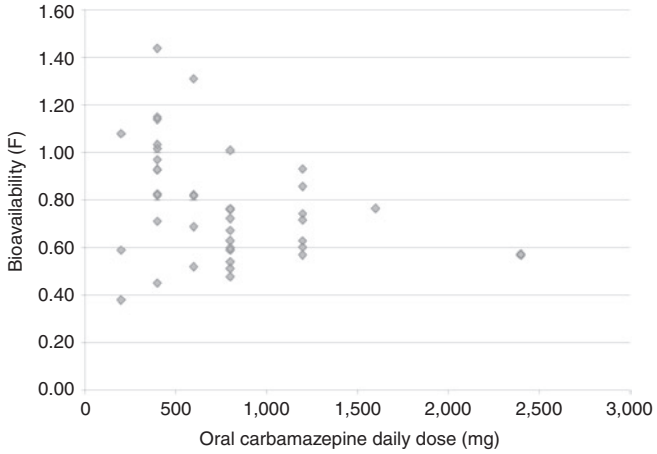

Figure 3 Distribution of carbamazepine bioavailability in relation to daily oral carbamazepine dose.

the polymorphisms are differentially expressed in Caucasians and African Americans,[24,32,33] with the latter being more likely to carry the wild-type form of 3A5, which confers greater enzymatic activity. Given that CBZ is a substrate for 3A5,[15,34] we hypothesized that the clearance rates in African Americans would be higher than those in Caucasians. Contrary to our expectations, we found that the Cl was 23% lower in African Americans than in Caucasians. It is possible that unknown 3A5 single-nucleotide polymorphisms are responsible for the unexpectedly low metabolism through this isoenzyme or that there is reduced activity in other metabolizing enzymes.

Although in this paper we do not directly address the role of genetics in producing the reported differences in Cl between Caucasians and African Americans, we considered other sources of variability that might have affected the mean Cl values for each population. The subjects were recruited from five sites, but 65% of the African Americans in the total sample were from one site, Miami. The majority (70%) of the subjects recruited in Miami were on an immediate-release formulation of CBZ (generic or Tegretol). On the other hand, patients from both the Emory University and Minnesota sites were largely (94 and 91%, respectively) taking extended-release formulations of CBZ (either Carbatrol or Tegretrol XR). Given that all the subjects were at steady-state, and that the induction process was complete, there is no obvious reason to postulate that the oral formulation would affect the clearance of intravenous CBZ. We therefore stratified the groups according to the site of recruitment and calculated the mean clearances of subjects at each site. Subjects at Miami had a lower Cl (0.038 ± 0.015 l/h/kg) than subjects from either Emory (0.052 ± 0.020 l/h/kg) or the three sites in Minnesota (0.049 ± 0.019 l/h/kg). In view of the finding that formulation as well as race are nested in site, there may be other (nongenetic) factors contributing to the unexpected difference in Cl between African Americans and Caucasians. Whatever the underlying mechanism(s), this finding warrants further investigation.

The mean elimination half-life in this study population averaged 20 h, exceeding the range of 12–17 h reported in the CBZ package insert for adult patients on monotherapy, and substantially longer than the estimate of 12 h reported by Eichelbaum[35] in four patients after 6 months of monotherapy. As with clearance, CBZ half-life also displayed wide intersubject variability, with a large percentage of the patients (26%) exhibiting a CBZ half-life of 24 h or longer. However, in 16% of the patients, the half-life of CBZ was ≤ 12 h. The almost sevenfold difference between the lower and upper limits of the range of elimination half-life values in this group of patients on CBZ monotherapy further emphasizes the need to tailor therapy to patient response.

Despite the presence of sex- and race-dependent differences in both Cl and elimination half-life, we found no difference in absorption rates across any of the groups. Although the average bioavailability per our results is at the lower limit of that reported in the package insert, our results indicate there is large interindividual variability in bioavailability. Because we withheld 100 mg of the morning oral dose, the resultant oral area under the plasma concentration–time curve $AUC_{0-\tau}$ slightly underestimates the actual AUC and, by extension, the true absolute CBZ bioavailability. The reduction in a single morning dose, averaging 39%, is likely to have had a modest effect (≈10%) on the oral AUC and estimation of bioavailability. However, a subsequent study, in which patients on oral CBZ were given intravenous CBZ as replacement therapy, found that the mean bioavailability was approximately 70% with variability comparable to that seen in our study.[36] The observation that some patients exhibited either very low absorption or had bioavailability values >1 suggests that there may be substantial intrapatient variability in CBZ absorption. Poor CBZ water solubility and slow absorption of the oral formulation may result in slowed and/or reduced CBZ absorption at certain times, followed by increased absorption of the current and recent doses depending on gastrointestinal conditions. Wide intrasubject variability in plasma CBZ concentrations, consistent with relatively abrupt changes in absorption, has also been reported by others.[37]

Both bioavailability and clearance can have a profound effect on CBZ dosing requirements. The results from our study indicate that, to attain a given target plasma drug concentration, patients with poor absorption and very high clearance may require doses as much as fivefold higher than patients at the opposite extremes of these parameters.

In conclusion, our study confirms that the determination of pharmacokinetics in healthy volunteers or after single doses may not accurately depict disposition under steady-state conditions. We found that, during maintenance therapy, CBZ absorption and clearance are highly variable, and its elimination half-life is longer than has been previously reported. These factors should be considered when managing CBZ therapy. In particular, given that Caucasian patients as compared with African-American patients, and women as compared with men, have, on average, 23–25% higher weight-adjusted clearance values, they may require a compensatory increase in mg/kg dosing. In addition, the clinician must be aware of the possibility that poor bioavailability and/or very high clearances, rather than noncompliance, may be the culprit when plasma CBZ levels do not reflect the

prescribed dose. Consequently, the results of our study can be used to guide more effective use of CBZ and suggest that rigorous characterization of other drugs during maintenance therapy might yield comparable information that can be clinically valuable.

METHODS

Subjects. The subjects were African-American and Caucasian men and women 18–64 years of age on a CBZ regimen for the treatment of epilepsy. The inclusion criteria for patients were either monotherapy with CBZ or CBZ alongside other medications that do not interact with it; a stable maintenance CBZ regimen, that is, receiving continuous dosing over multiple months; and no dosage adjustments in CBZ, not even minor changes, within the 2 weeks prior to the first day of the study. Enrollment was stratified with the intention of studying equal numbers of women and men and also equal numbers of Caucasians and African Americans. Those with significant medical problems (who might not have been able to tolerate intravenous administration of CBZ), those taking medications known to affect CBZ disposition, and those who reported nonadherence to their CBZ therapy regimen were excluded from the study. Prior to enrollment, the project coordinator contacted potential subjects to discuss the protocol, confirm drug therapy, and review the consent form. The study was performed at the general clinical research centers of the participating institutions, or equivalent facilities.

The study protocol was approved by the institutional review boards for the five clinics from which subjects were recruited: University of Minnesota, MINCEP Epilepsy Care, Minneapolis VA Medical Center, Emory University, and the University of Miami. All subjects provided written informed consent. The study was conducted in accordance with FDA IND 60,722, "Use of an Intravenous Stable-labeled Carbamazepine Isotope in Adult and Elderly Patients," 2000.

Intravenous, stable-labeled CBZ formulation. Stable-labeled CBZ (SL-CBZ (5H-dibenz[*b,f*]azepine-5-^{13}C, ^{15}N-carboxamide)) was synthesized at Isotec/Sigma-Aldrich (Miamisburg, OH). The labels included ^{13}C and ^{15}N. The SL-CBZ was dissolved in a 22.5% wt/vol solution of HP-β CD to yield a 10 mg/ml solution of SL-CBZ. The intravenous formulation was prepared, using good manufacturing practices, at the University of Iowa Division of Pharmaceutical Services.

Study design. The study was carried out using an open-label design. The subjects were instructed to fast overnight before the morning of commencement of the study and not to take their morning doses of drugs. On the morning of the study, the patients were admitted to a research center, where they underwent brief medical and neurological exams and their seizure and medication histories were recorded. An indwelling catheter was then inserted in the left arm to facilitate blood sampling throughout the entire stay (either 12 or 24 h). Blood samples were collected for genotyping, blood chemistries, and recording of blood urea nitrogen , CO_2, glucose, creatinine, bilirubin, albumin, and α-1-acid glycoprotein levels. A second catheter was placed in the right arm for delivery of the study drug and was removed 1 h after infusion.

For drug delivery, a syringe was filled with 10 ml of the investigational formulation, weighed, and placed on an infusion pump. The 100-mg SL-CBZ dose was infused over a period of 10 min. Central nervous system toxicity and electrocardiogram were assessed by a neurologist (I.E.L., J.R.W., P.B.P., R.E.R.) prior to, during, and 20 min after the infusion. Blood pressure and pulse were monitored every 2 min during infusion, every 15 min after infusion, and then every 8 h for 12 or 24 h after infusion (depending on length of stay). A research nurse periodically examined the infusion site for irritation and extravagation, and asked the patient about infusion site discomfort. The safety data from this study have previously been reported.[38]

At the end of the infusion, the syringe was weighed again to confirm the amount of drug actually delivered. Immediately after receiving the SL-CBZ, the patient took his or her usual morning CBZ oral dose minus 100 mg (and also any other medications and/or supplements normally taken in the morning).

Blood sampling and drug analysis. Blood samples for determination of CBZ and CBZ-E were drawn prior to drug delivery, and at 5, 15, 30 min, and 1, 2, 4, 6, 12, 24, 48, 72, and 96 h after administration of SL-CBZ. The samples were immediately centrifuged and the plasma was frozen and stored until analysis. Urine samples were collected over a period of 12 h or 24 h after the administration of SL-CBZ, depending on the length of stay of the subject in the research facility. After this initial inpatient stay, the blood samples at later time points were collected either at the inpatient site or at a local clinic.

Concentrations (bound and unbound) of the unlabeled and SL-CBZ and the unlabeled metabolites of CBZ (epoxide and diol) in plasma were measured using ESI and SIM modes of liquid chromatography–mass spectrometry (Agilent 1100 LCMSD with Electrospray, model G1946; Agilent Technologies, Santa Clara, CA).

A volume of 1.0 ml of each subject sample was spun in an Amicon Centrifree filter assembly (Millipore, Billerica, MA) at 37 °C to remove proteins along with the bound CBZ, and the filter assembly containing plasma was centrifuged using a fixed-angle rotor at 2,000 rpm for 60 min. If the ultrafiltrate volume was <500 µl, the sample was spun for an additional 15–30 min. The samples were then prepared by adding 500 µl of the plasma ultrafiltrate to 20 µl of CBZ-d10 (internal standard: 250 µg/ml solution), and extracted by adding 2.0 ml ethyl acetate to each sample and vortexing for 20 s. Each tube was then centrifuged for 10 min at 2,000 rpm, and the organic layer was transferred to a clear test tube and dried on a Zymark (Hopkinton, MA) evaporator at 30 °C for 15 min. The samples were reconstituted with 200 µl of mobile phase consisting of ammonium acetate buffer and methanol. The buffer was prepared with 3.85 g ammonium acetate (reagent grade) in 1 l water and the pH was adjusted to 4.7 using glacial acetic acid. After combining 1 l buffer with 1 l methanol, the mixture was filtered and degassed prior to use. After the addition of the mobile phase, the samples were filtered using a tuberculin syringe and a 0.2 µ syringe filter, and transferred to prelabeled, auto sampler vials.

The analytes were separated using a Zorbax LC8 column (3.0 × 150 mm, 3.5 µ; Agilent Technologies) at 40 °C and the mobile phase (described above). The data were generated using Agilent ChemStation software (Agilent Technologies) and quantified using a deuterated CBZ-d10 internal standard, with a molecular weight of 246 (C/D/N Isotopes, Quebec, Canada, cat. no. D-3542), and quadratic curves. The SL-CBZ was monitored at a molecular weight of 238 vs. 236 for unlabeled CBZ. The samples were run along with a 7-concentration standard curve (run in triplicate) (range: 0.5–20 µg/ml for the total unlabeled CBZ; 0.1–4 µg/ml for remaining analytes) and with three quality-control samples (low, medium, and high), which were also run in triplicate. Unextracted samples of CBZ and SL-CBZ were also run for each assay to determine whether there was any contribution of unlabeled CBZ to SL-CBZ, and vice versa. It was found that there was no contribution of unlabeled CBZ to SL-CBZ. The contribution of SL-CBZ to unlabeled CBZ was ~1.5%, which is consistent with the amount of naturally occurring ^{13}C. Each analytical run was corrected by the amount determined from that day's assay.

The method was validated in our laboratory, and had a within-assay variability <5.0% for all standards and a between-assay variation <5% for all standards except for the lowest standard, for which it was 14.5%. Accuracy ranged between 83.7 and 102.6% for all standards. Quality-control samples were all within ≤10% with respect to variability.

Pharmacokinetic analyses. The concentration–time data for both stable-isotope and nonlabeled CBZ were analyzed using the pharmacokinetic modeling program WinNonLin 5.1, employing nonlinear regression and a noncompartmental model assuming first-order absorption and elimination.

For each subject, the terminal log-linear phase of the SL-CBZ plasma concentration–time curve was identified, and the elimination rate constant (k_e) was determined by regression analysis based on at least

five time points. The elimination half-life ($t_{1/2}$) was then calculated from the following equation: $t_{1/2} = \ln 2/k_e$.

The AUC was calculated using the logarithmic trapezoidal rule with extrapolation to infinity (AUC(0–∞)) for intravenous SL-CBZ, using k_e. The logarithmic trapezoidal rule was also used to calculate the $AUC_{oral\ (0-\tau)}$. Values for absolute plasma clearance and volume of distribution (V_d) of SL-CBZ were calculated by noncompartmental methods as follows:

Clearance = Dose/AUC_{INF_obs} and V_d = Dose/($k_e AUC_{INF\_obs}$). Values for free fraction (Fμ) were calculated as free CBZ/total CBZ.

The absolute bioavailability (F) of oral CBZ was estimated from the data of 42 subjects who were taking a fixed dose per dosing interval of oral CBZ, either every 8 h or every 12 h. F was calculated using the following equation:

$$F = \frac{AUC_{oral\ (0-\tau)}}{AUC_{i.v.\ (0-\infty)}} \times \frac{\text{i.v. dose}}{\text{oral dose}}$$

Statistical analysis. The effects of sex and race on elimination half-life, clearance values adjusted for weight (l/h/kg), and volume of distribution (l) were examined using a univariate analysis of variance (SPSS, v.14). A value of $P \leq 0.05$ was considered significant.

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CONFLICT OF INTEREST

I.E.L., J.C.C., and A.K.B. have a royalty agreement with Lundbeck Inc. related to the development of intravenous carbamazepine. The other authors declared no conflict of interest.

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