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Characterization of the Time Course of Carbamazepine Deinduction by an Enzyme Turnover Model

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Abstract

Background and objective—Carbamazepine is a potent inducer of drug metabolizing enzymes, which results in a number of clinically significant drug-drug interactions. Deinduction occurs when chronic carbamazepine therapy is discontinued. The goal of this study was to develop a population pharmacokinetic model to describe the time course of carbamazepine deinduction.

Patients and methods—Stable-labeled carbamazepine was administered intravenously on three occasions during the deinduction period to fifteen patients with epilepsy for whom carbamazepine therapy was being discontinued. Data were analyzed using a nonlinear mixed effect model (NONMEM). An enzyme turnover model consisting of a one compartment model linked with a hypothetical enzyme compartment was applied to characterize the time course of carbamazepine deinduction. Model evaluation was performed using the bootstrap approach and visual predictive check.

Results—In the final model, the deinduction process was accomplished by decreasing the rate of enzyme synthesis resulting in a decrease in the relative amount of enzymes. The estimated rate constant for enzyme degradation was 0.00805 hr⁻¹, corresponding to a half-life of the combined enzymes of 86.1 hours (3.6 days).

Conclusions—An enzyme turnover model adequately characterized the experimental data. Based on the predicted enzyme half-life from the final model, the deinduction process should be completed within 2 weeks after carbamazepine therapy is terminated.

Keywords

NONMEM; carbamazepine; deinduction; population pharmacokinetics

BACKGROUND

Carbamazepine (CBZ) is commonly prescribed for the treatment of epilepsy, bi-polar disorder, and trigeminal neuralgia.[1] Therapy with CBZ is complicated by its complex pharmacokinetics and drug-interaction profile. CBZ is primarily metabolized to

carbamazepine-10,11-epoxide (CBZ-E) by the cytochrome P450 (CYP)3A4 isoenzyme. As a potent inducer of several drug transporters and drug-metabolizing enzymes including multiple CYP450 and UGT isoenzymes,[2] CBZ can affect the disposition of other agents. Moreover, CBZ is one of the few drugs that, after multiple doses, can stimulate the synthesis of enzymes that catalyze its own metabolism by a process known as autoinduction.[3-5] An increase in gene transcription resulting in an elevated level of drug metabolizing enzymes is thought to be the major mechanism of autoinduction.[6] Deinduction, the reverse process of autoinduction, occurs when chronic CBZ therapy is discontinued. An understanding of the time course of CBZ deinduction is necessary in order to optimally adjust CBZ and co-medication dosing regimens when reducing or terminating CBZ therapy.

An enzyme turnover model has been applied to several drugs in humans in order to characterize the time course of autoinduction.[7-11] This model links the hypothetical enzyme compartment with the drug compartment by allowing drug clearance to be affected by the amount of enzyme. The amount of enzyme is regulated by a zero order rate of enzyme production and a first order rate of enzyme degradation. During induction, the enzyme amount increases by increasing the rate of enzyme production or by decreasing the rate of enzyme degradation. Conversely, during the deinduction process, the enzyme amount can be decreased by either decreasing the rate of enzyme production or by increasing the rate of enzyme degradation. The half-life of the induced enzymes, an important parameter for characterizing the time course of both autoinduction and deinduction, can be estimated from this model.[7,10,11]

The aim of this study was to develop a population pharmacokinetic enzyme turnover model that would describe the time course of CBZ deinduction under clinical conditions. This was accomplished by using a novel stable-labeled CBZ formulation that could be administered intravenously. The use of an intravenous formulation avoids the problems associated with variable absorption whereas the stable-label provided us with the means to measure a tracer amount of drug enabling measurement of CBZ over a very short duration of time. This information can provide evidence-based guidelines for management of drug therapy when CBZ is discontinued.

METHODS

Patients and treatments

Data from fifteen patients with epilepsy receiving oral CBZ therapy in whom CBZ was being discontinued were recruited from epilepsy clinics in Minneapolis, MN, Miami, FL, and Atlanta, GA metropolitan areas. All subjects provided signed consent. The study was approved by the human subjects committee at each of the study sites and at the University of Minnesota. Patients were excluded from the study if they were on comedications that were known to interact with CBZ. On the day of the study, patients were admitted to a clinical research center at the respective sites. A 10-minute intravenous infusion of a 100 mg dose of an investigational, stable-labeled CBZ (SL-CBZ) formulation was administered on three occasions: 1) the morning after the last dose of oral CBZ (mean dose = 140 mg $\pm$ 50.7 mg), 2) 6-8 days after the last oral CBZ dose, and 3) 6-8 weeks after the last oral CBZ dose. Serial plasma SL-CBZ concentrations were measured following SL-CBZ administration at each occasion.

Blood sampling and assays

Fourteen blood samples were collected prior to drug administration and at 0.083, 0.25, 0.5, 1, 2, 4, 6, 10, 12, 24, 48, 72, and 96 hours after the end of the SL-CBZ infusion. The blood samples were immediately centrifuged and plasma was stored frozen until analysis. SL-CBZ concentrations were determined using liquid chromatograph-mass spectrometry (Agilent 1100 LCMSD with Electrospray, G 1946). Briefly, prepared samples were dried and reconstituted

with ammonium acetate buffer and methanol as a mobile phase. CBZ-d₁₀ was used as an internal standard. The samples were then separated using a Zorbex LC8/LC18 column (Agilent Technologies). Data were generated using Agilent ChemStation software (Agilent Technologies, Palo Alto, CA) and quantified using deuterated CBZ-d₁₀ internal standard via a validated assay in our research laboratory.

Population pharmacokinetic analysis

Plasma SL-CBZ concentrations were fitted to a one-compartment model with a hypothetical enzyme compartment[7,9] to describe CBZ deinduction pharmacokinetics as presented in Figure 1.

The change in the amount of CBZ (A_1 , mg) over time can be described by equation 1,

$$\frac{dA_1}{dt} = k_0 - CL * C_p * A_2, \quad \text{equation (1)}$$

where k_0 is the rate of infusion (mg/hr), CL is CBZ clearance (L/hr), C_p is CBZ plasma concentration (mg/L), and A_2 is the proportion of enzymes at time t relative to the total enzymes at time zero in the hypothetical enzyme compartment. CBZ clearance is considered proportional to the amount of enzymes in a hypothetical enzyme compartment.

The deinduction process is often the result of a decrease in the rate of enzyme production, a reverse process of induction, leading to a decrease in the amount of all enzymes[12]. Therefore, our chosen model was the model in which the change of the relative amount of enzymes in a hypothetical enzyme compartment (A_2) can be characterized by equation 2,

$$\frac{dA_2}{dt} = k_{enz,in} * (1 - \text{FACTOR}) - k_{enz,out} * A_2, \quad \text{equation (2)}$$

where $k_{enz,in}$ (relative amount/time) is the zero-order rate constant for enzyme production, $k_{enz,out}$ (time⁻¹) is the first-order rate constant for the enzyme degradation, and FACTOR describes the fractional decrease of enzyme production rate. The apparent half-life of the CBZ deinduction process was estimated by dividing $\ln(2)$ by $k_{enz,out}$. Before the deinduction process ($t=0$), the enzyme amount was assumed to be at steady state and was normalized to 1; therefore, the rate of production is equal to the rate of enzyme degradation. In this model, the deinduction process was assumed to begin at the first SLCBZ administration (the next morning after the last dose of CBZ). It is possible that the starting time of the deinduction process may impact the estimate of the half-life of the enzymes. Therefore, a sensitivity analysis from time 0 (the start of SL-CBZ infusion) to 48 hours was performed to determine the effect of various starting times of the deinduction process on the estimate of $k_{enz,out}$. The models with the assumed starting time of the deinduction process at 0, 5, 10, 15, 20, 24 and 48 hours after the start of SL-CBZ infusion were fit to the data and the estimates of $k_{enz,out}$ were recorded.

Data from all three occasions were analyzed using the nonlinear mixed-effect modeling program (NONMEM), subroutine ADVAN 6 (version VI, NONMEM Project Group, UCSF/Globomax and PDx-Pop version 2.0). The first-order conditional estimation method with interaction (FOCE-I) was used for all analyses. Inter-individual variability (IIV) was modeled using an exponential error model for all parameters. The residual unexplained variability (RUV) was modeled using a proportional error model. Discrimination between hierarchical models was determined based on the difference in objective function value (OFV) using the likelihood ratio test and visual inspection of diagnostic plots. A drop in objective function value

(OFV) of at least 10.83 ($p < 0.001$, χ^2 , $df = 1$) after adding one parameter was considered statistically significant.

Initially, the model was developed without any covariates (base pharmacokinetic model). Due to the small sample size in this study, only weight was tested as a covariate. The covariate model was built in a stepwise fashion. Weight, centered at a convenience weight of 80 kg, was added on each parameter (CL, Vd, and $k_{enz, out}$) one at a time using a linear covariate model. A decrease in OFV of at least 6.64 ($p < 0.01$, χ^2 , $df = 1$) was used to determine the inclusion of weight on each parameter. The full model was developed by including all significant weight-parameter relationships. From the full model, weight was deleted from each parameter one at a time to obtain the final model. An increase of OFV from the full model of at least 10.83 (χ^2 , $p \leq 0.001$, $df=1$) was used as the chosen criteria for retaining weight-parameter relationships in the covariate model. Xpose[13] and S-plus 2000 (Insightful Corp, Seattle, WA, USA) were used for graphical model diagnostics.

Several possible models other than the chosen model were considered: i) a model where the deinduction process was characterized by increasing the rate of enzyme degradation rather than decreasing the rate of enzyme production, ii) a model describing autoinduction of CBZ in which an increase of enzyme amount is described by a linear relationship between CBZ concentrations and the rate of enzyme production, and iii) a model describing autoinduction of CBZ in which an increase of enzyme amount is described by an Emax relationship between CBZ concentrations and the rate of enzyme production.

Model evaluation

Model evaluation was assessed using the nonparametric bootstrap method and a visual predictive check (VPC). The nonparametric bootstrap re-sampling technique was applied for assessing the reliability of the parameter estimates and their 95% confidence intervals (CI). [14,15] Five hundred bootstrap data sets were generated by repeatedly sampling with replacement from the original data set using Wings for NONMEM (Version 600, <http://wfn.sourceforge.net>). The final model was fit to each of 500 bootstrap data sets, therefore parameter estimates were obtained from each data set. These parameter estimates were rank ordered. The values at 2.5th and 97.5th percentile were used to estimate a bootstrap 95% CI for the estimates and were compared with the values obtained from NONMEM.

The visual predictive check was used as a diagnostic tool to assess the adequacy of the model. [16,17] Five hundred data sets were simulated with the same study design using the final model parameter estimates obtained from NONMEM. The median and 90% prediction intervals (5th and 95th percentile) of the simulated concentrations were calculated at each time point and plotted against the observed concentrations.

RESULTS

A total of 524 SL-CBZ concentration-time points from fifteen patients were used in this study. Six women and nine men with a mean weight of 78 kg and age of 39 years participated in the study. Fourteen patients completed all three occasions of the study whereas one patient only completed the first two occasions. Data from all fifteen patients were included in the analyses. Figure 2 presents the observed CBZ concentration-time curves and variability for each individual at each occasion.

Of the models explored, the one that described the deinduction process as a fractional decrease in the rate of enzyme production best described the data. A model where the deinduction process was characterized by an increasing rate of enzyme degradation described the data as well as the chosen model based on the OFV and goodness-of-fit plots. However, this model is

not as physiologically plausible as the chosen model. The concentration-dependent autoinduction models, both linear and Emax models, were not able to fit the data. The model with the linear increase in the rate of enzyme production resulted in unreasonable parameter estimates and it was not possible to obtain the parameter estimates from the Emax type model (data not shown).

Weight was tested as a covariate on V_d , CL , and $k_{enz, out}$. V_d was the only parameter indicated to have a significant relationship with weight. The addition of V_d to the model resulted in a drop in OFV from the base model (the difference in OFV = -19.7) and an improvement in the goodness-of-fit plots compared with the base pharmacokinetic model (Figure 3). Therefore, the effect of weight on V_d was included in the final model. The final parameter estimates are presented in Table I. Based on the $k_{enz, out}$ estimate of 0.00805 hr^{-1} , the model predicted apparent half-life of the deinduction process was 86 hours (3.6 days). Adding IIV into $k_{enz, out}$ or FACTOR did not improve the fit. Therefore, $k_{enz, out}$ and FACTOR were estimated without an estimate of IIV. Not being able to determine variability for an estimated parameter is not unusual if the data are limited and do not allow partitioning of the variability. The results from the sensitivity analysis showed that when the starting time of the deinduction process was varied from 0 to 48 hours, the estimated rate constants for the enzyme degradation were not different (estimates of $k_{enz, out}$ ranged from 0.008 to 0.0087). These results indicate that the assumed starting time points have a small impact on the estimation of $k_{enz, out}$.

Model evaluation

The reliability of the final parameter estimates were confirmed by re-estimating the model parameters and their 95% CI using a nonparametric bootstrap approach. From 500 bootstrap runs, 493 were minimized successfully and were included in the bootstrap analysis. The median parameter estimates and their 95% CI obtained from 500 bootstrap data sets were comparable to the estimates obtained from NONMEM (Table 1). However, the 95% CI of $k_{enz, out}$ obtained from the bootstrap approach was wider than the one obtained from NONMEM. This situation is common when the size of sample is small[18]. As the 95% CI obtained from NONMEM assumes the asymptotic normality, this assumption is true when the sample size is large enough. Therefore, in a small data set, the bootstrap 95% CI can be wider than the one obtained from NONMEM.

The visual predictive check was used to assess the model performance for the population pharmacokinetic model. Figure 4 (a-c) presents visual predictive check plots. These plots show that most of the observed concentrations on all three occasions fell within 90% prediction intervals obtained from the simulated data represented by the shaded area. Less than 10% of the observed concentrations lie outside the specific prediction intervals. The results from the visual predictive check show that the final model adequately describes the majority of the observed data in this population.

DISCUSSION

This study is the first to use an intravenous formulation to characterize the deinduction half-life of CBZ in patients with epilepsy. This use of an intravenous formulation avoided issues associated with variable absorption of the drug. Furthermore, our results demonstrate that the time course of CBZ deinduction can be adequately described by an enzyme turnover model. This model yields an estimate of the half-life of the deinduction process from which the time course of CBZ deinduction can be determined. It should be noted that this estimated half-life of enzyme turnover is a hybrid value encompassing all isoenzymes involved in CBZ metabolism rather than any particular isoenzyme.

The mechanism underlying autoinduction/deinduction of CBZ is not well understood. It has been postulated that autoinduction of CBZ metabolism occurs by increasing the synthesis of enzyme (*de novo* protein synthesis).[2] There is evidence that both CBZ and CBZ-E can activate the nuclear receptor, PXR (pregnane X receptor), resulting in a higher expression level of mRNA of numerous enzymes including several CYP genes, conjugated enzymes, and transporters.[2] Deinduction is believed to occur via the reverse process of autoinduction. Based on current understanding of the mechanism of CBZ deinduction, the model used in this study, which is based on a decreasing rate of enzyme production is more physiologically plausible than a model with an increasing rate of enzyme degradation.

In the situations in which the elimination half-life of an inducer is similar to or longer than the induced enzymes, the pharmacokinetics of the inducer may impact the accurate estimation of a half-life of the induction/deinduction process; therefore, pharmacokinetics of the inducer cannot be ignored.[19] However, in the case where the elimination half-life of an inducer is considerably faster than the half-life of the induced enzymes, the kinetics of the inducer will have minimal effect on the estimated half-life of the induction/deinduction process. Hence, the time course of the induction and deinduction processes is determined by the same rate constant of enzyme degradation.[19] The rate constant for the enzyme degradation estimated from our model was 0.00805 hr^{-1} , corresponding to an overall enzyme half-life of 3.6 days (86.1 hours), whereas the elimination rate constant of CBZ in the induced state was estimated to be 0.048 hr^{-1} , corresponding to a CBZ half-life of 15 hours. These values are consistent with the enzyme half-life reported in previous studies of CBZ autoinduction/deinduction.[11,20-22]

In our study, the estimate of CBZ half-life is much faster than the estimated enzyme half-life; therefore, the all-or-none model used in our study, where the pharmacokinetics of the inducer was not incorporated in the model, should adequately describe the data. It is possible that a longer half-life of CBZ during the deinduced state may be observed. However, even if the half-life of CBZ doubled it would still be much shorter than the half-life of the induced enzymes. Therefore, with the relatively rapid elimination of CBZ during the deinduction process compared with the turnover half-life of the enzymes, the effect of CBZ kinetics on the estimate of the enzyme degradation rate constant should be negligible. A previous study that used probe substrates to determine the CBZ-mediated induction of CYP3A4 and CYP1A2 separately obtained estimated half-lives of CYP3A4 and CYP1A2 of 70 and 105 hours, respectively. [11] The estimated half-life of enzymes obtained from our study following administration of an intravenous formulation is within this range.

The model used in this analysis assumed that the deinduction process started when the first dose of SL-CBZ was given ($t=0$). Bernus et al.[23] speculate a 1-2 day lag time in the deinduction process of CBZ. Therefore, different starting times of the deinduction process, varying from time 0-48 hours, were tested in the sensitivity analysis. The results from our sensitivity analysis indicate that the time that deinduction begins has a minimal effect in the estimate of $k_{\text{enz, out}}$. It is also possible that the first two doses of SL-CBZ could delay the deinduction process causing a slight increase in the deinduction half-life; however, we believe this effect to be minimal.

CONCLUSION

In summary, a population pharmacokinetic model characterizing the time course of CBZ deinduction was developed using an enzyme turnover model. The bootstrap approach and visual predictive check confirmed the reliability and adequacy of the final model. Based on a $k_{\text{enz, out}}$ estimate of 0.00805 hr^{-1} , induction of CBZ metabolizing enzymes is reduced by half at 3.6 days and by three-fourths at 7.2 days after CBZ is completely discontinued. Therefore, the deinduction process should be completed within 2 weeks after discontinuation of CBZ

therapy. There are several clinical implications that arise from our results. The doses of a number of important drugs such as hormonal contraceptives may need to be adjusted within 3-6 days following discontinuation of CBZ. Also, it is common to discontinue CBZ during monitoring of persons with epilepsy in inpatient diagnostic units. To the extent that deinduction is the inverse process of induction, the results from this study can be important in estimating the optimal doses of CBZ when it is reintroduced after being held for seizure monitoring.

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Figure 1.

Pharmacokinetic model of CBZ de-induction. The model represents a one-compartment model with a hypothetical enzyme compartment. The amount of CBZ (A_1) is determined by rate of infusion (k_0) and elimination rate constant (CL/V_d). The relative amount of enzyme (A_2) in a hypothetical enzyme compartment is characterized by a rate constant for enzyme production ($k_{enz, in}$) and a rate constant for enzyme degradation ($k_{enz, out}$).

Figure 2.

The individual observed concentration time curves of SL-CBZ at each occasion

Figure 3.

The goodness of fit plot; the observed versus population model predicted concentrations and weighted residuals versus population model predicted concentrations of the base model and the final model (adding weight into V_d)

(a) occasion 1 **(b) occasion 2** **(c) occasion 3** **Figure 4.**

The visual predictive check plots for occasion 1 (a), occasion 2 (b), and occasion 3 (c). The solid lines and shaded area represent median and 90% prediction interval from 500 simulated data. The circles represent the observed concentrations.

Table I

Final model parameter estimates and 95% confidence intervals (CI) from NONMEM and the bootstrap analysis

Parameters	NONMEM*		Bootstrap Analysis†	
	Estimates	95% CI	Median	95% CI
Initial clearance (L/hr)	3.05	[2.62, 3.48]	3.06	[2.67, 4.93]
Vd (L)	64.3	[59.2-69.4]	64.1	[58.54, 70.63]
Coefficient for weight on Vd	0.869	[0.57-1.17]	0.863	[0.5, 1.22]
First order rate constant for enzyme degradation ($k_{enz, out}$)	0.00805	[0.003-0.0128]	0.0082	[0.005, 0.066]
FACTOR	0.494	[0.438-0.55]	0.497	[0.43, 0.7]
IIV for initial clearance (%CV)	31.6	[19.52-40.52]	30	[18.4, 39.8]
IIV for Vd (%CV)	17.5	[12.57-21.4]	16.16	[9.54, 20.86]
RUV, proportional (%CV)	26.9	[24.7-29.77]	26.7	[23.48, 29.79]

* (Estimate) $\pm 1.96 \times$ (standard error of the estimate)

† values at 2.5th and 97.5th percentile of the ranked bootstrap parameter estimates IIV, interindividual variability; RUV, residual unexplained variability; %CV, percent of coefficient of variation; $k_{enz, out}$, first order rate constant for enzyme degradation.