Population pharmacokinetics of lamotrigine monotherapy in patients with epilepsy: retrospective analysis of routine monitoring data

Z. Hussein & J. Posner

Department of Clinical Pharmacology, GlaxoWellcome Research and Development, UK

Aims To examine the population pharmacokinetics of lamotrigine in patients newly diagnosed with epilepsy and receiving oral lamotrigine monotherapy for up to 48 weeks.

Methods The population consisted of 158 Caucasians and 5 Asians of whom 81 were males and 82 females. Age and weight ranged between 14 and 76 years and 41–107 kg, respectively. A one-compartment model with first-order absorption and elimination was fitted to plasma lamotrigine concentration–time profiles from retrospective drug monitoring, using non-linear mixed effect modelling (NONMEM), with first-order estimation. Oral clearance (CL_o), apparent volume of distribution (V/F) and absorption rate constant (K_a) were the main pharmacokinetic parameters.

Results CL_o was not significantly influenced by body weight, age, gender, oral contraceptives and dose. However, due to auto-induction CL_o increased by 17.3% during the 48 weeks of therapy, from 1.94 to 2.28 l h⁻¹, and was 28.7% lower in Asians than Caucasian. The final magnitude in interpatient variability was 32%. The effect of the covariates weight, age, race and gender on V/F was examined and none was statistically significant. The final population estimate of V/F was 77.4 l with an interpatient variability of 34%.

Conclusions In view of the wide therapeutic margin of lamotrigine and the 21% residual variability in plasma concentrations, the modest significant effects of race and auto-induction on clearance are unlikely to be clinically significant and, thus, no dosage adjustment is warranted for these effects.

Keywords: lamotrigine, epilepsy, monotherapy, NONMEM, population, pharmacokinetics

Introduction

Lamotrigine (Lamictal®) is a novel antiepileptic drug which is chemically unrelated to existing antiepileptic drugs. It is thought to act by blockade of voltage-sensitive sodium channels and inhibition of glutamate release [1, 2]. The efficacy of lamotrigine monotherapy and add-on therapy with other existing antiepileptic drugs has been demonstrated in a series of double-blind, placebo-controlled, cross-over trials in hundreds of patients with refractory partial seizures, with or without focal and generalised tonic-clonic seizures [3–8].

The single and multiple dose pharmacokinetics of lamotrigine monotherapy have been extensively investigated in healthy young and elderly volunteers [9–12], patients [13–15], volunteers with Gilbert's syndrome [16], and volunteers with chronic renal failure [17]. Oral lamotrigine is rapidly and completely absorbed, reaching peak plasma concentrations within 2.8 ± 1.3 h, with linear pharmacokinetics described by a one-compartment open model with first-order absorption and elimination. Multiple dosing to volunteers is associated with mild auto-induction [18]. About 70% of an oral dose is recovered in urine with glucuronide conjugates accounting for almost 90% of the

urinary recovery. In healthy volunteers and patients receiving lamotrigine monotherapy, mean half-life ranges from 23 to 37 h, but is reduced to about 15 h with concomitant administration of enzyme-inducing antiepileptic agents such as phenobarbital, phenytoin or carbamazepine. Due to competition for glucuronidation, co-administration with valproate prolonged lamotrigine half-life to 48.3 to 59 h. Compared with healthy volunteers, in chronic renal failure lamotrigine clearance was similar but elimination half-life and the volume of distribution were slightly higher and renal clearance was 50% lower [17].

The present report examines the population pharmacokinetics of lamotrigine utilising routine monitoring plasma concentration data in patients newly diagnosed with epilepsy and undergoing lamotrigine monotherapy for up to 48 weeks. The effects of demographic factors, dose, the oral contraceptives and duration of therapy on lamotrigine pharmacokinetics were investigated.

Methods

Study population

Data were obtained retrospectively from three Phase II/III clinical trials. Inclusion criteria into the trials specified the seizure type as partial or generalised tonic-clonic in a patient

Correspondence Dr Ziad Hussein, Centre for Applied Pharmacokinetic Research (CAPKR), School of Pharmacy and Pharmaceutical Sciences, The University of Manchester, Oxford Road, Manchester M13 9PL, UK.

diagnosed as suffering from epilepsy (not due to a reversible causal factor such as antidepressant drugs) with a frequency of at least two epileptic seizures in the last 6 months and at least one seizure in the last 3 months. Patients were excluded from the trials if suffering from absence seizures, psychiatric disease, severe mental subnormality ($IQ < 70$), acute or progressive neurological disease, or other disease likely to interfere with the objectives of the study. Patients also excluded were those with abnormal haematology and biochemistry values at screen, previously treated with any antiepileptic drugs for epilepsy, on any chronic medication other than oral contraceptives, abusing alcohol and/or other substances, pregnant, lactating or exposed to risk of pregnancy. Written informed consent was obtained from all patients and additionally from parents or guardians for those patients under 18 years of age or considered incompetent. All patients were healthy, apart from their epilepsy, with normal hepatic and renal functions.

Study designs and dosing

All three Clinical Phase II/III trials were multicentre, double-blind, parallel group trials comparing lamotrigine with either phenytoin or carbamazepine for up to 48 weeks. In one trial patients assigned to receive lamotrigine were initially scheduled to receive 100 mg once daily at night for the first 2 weeks followed by 150 mg once daily at night for the following 2 weeks. The other two trials were identical in design and patients assigned to receive lamotrigine were scheduled initially for 50 mg once daily at night during week 1, 50 mg twice daily for week 2, followed by 50 mg in the morning and 100 mg in the evening throughout weeks 3–48.

In all three trials, the dose was adjusted by the investigators at the end of weeks 4, 6, 8, 12, 18 and 24 based on efficacy, safety, and plasma concentration data. In patients where no dose adjustment was necessary, they were dosed as for week 4 throughout the trial. Dosing frequency was adjusted according to the number of tablets/capsules required per day as specified in the study protocols.

Blood sampling and lamotrigine assay

During the 48 weeks treatment phase, visits for clinical assessment were scheduled at the end of weeks 1, 2, 4, 6, 8, 12, 18, 24 and 48. As part of the clinical assessment, blood samples were scheduled to be taken at each visit when patients were required to provide the exact time of the last dose relative to the sampling time. Sampling was generally spread within the dosing intervals starting 0.5 h relative to the last dose. Plasma was separated and stored at below -10°C until assayed for lamotrigine by using a validated high performance liquid chromatography procedure with a lower detection limit of $0.1\text{ }\mu\text{g ml}^{-1}$. Recovery of lamotrigine from plasma was approximately 90%, whereas within-day and day-to-day coefficients of variation for quality control samples were between 4 and 10%.

Database construction

In generating the NONMEM database, each patient's dosing regimen was constructed for the entire treatment period of

up to 48 weeks, and steady-state was not assumed. However, the actual times of dosing were not reported in the case report forms except for the last dose prior to each visit to the clinic; therefore, dosing intervals of 24, 12 and 8 h were assumed for once, twice and thrice daily dosing regimens, respectively. Concentration data from blood samples reported to be taken more than one dosing interval after the last dose were not included in the database. Additionally, data with inadequate documentation of the dosing regimen and/or sampling time were excluded from the analysis. During the preliminary analysis, obvious outlier concentrations (more than two-fold lower or higher than other concentrations for that individual) were deleted from the database.

Pharmacokinetic analyses

Plasma concentration-time profiles in the database were used for non-linear mixed effect modelling by extended least squares regression using the NONMEM computer program (Version IV, level 2.0), with double precision and first-order estimation [19], installed on an IBM 3090–300J computer. A one-compartment open model with first-order absorption and elimination, a model previously found to describe lamotrigine plasma profiles adequately after oral administration to healthy volunteers, was fitted to lamotrigine plasma concentration-time profiles. The fundamental pharmacokinetic parameters used to characterise the one-compartment model were apparent oral clearance (CL_o), apparent volume of distribution (V/F), and absorption rate constant (K_a). The magnitudes of interpatient variability in parameters, such as CL_o , were modelled as follows:

$$CL_j = TVCL \cdot (1 + \eta_{j,CL})$$

where: CL_j is the value for CL_o for the j^{th} individual; TVCL is the population mean value for CL_o ; and $\eta_{j,CL}$ was assumed to be a random Gaussian variable with zero mean and variance ω_{CL}^2 that distinguished the j^{th} individual's parameter from the population mean as predicted by the regression model [19, 20]. The magnitude of interpatient variability in CL_o was, thereafter, expressed as a coefficient of variation (CV). The magnitude of interpatient variability in V/F was modelled similarly; interpretation of this model is analogous to that for CL_o .

The magnitude of residual variability in plasma concentrations was modelled using the following proportional error model:

$$C_{\text{obs},ij} = C_{\text{pred},ij} \cdot (1 + \epsilon_{ij})$$

where, $C_{\text{obs},ij}$ is the i^{th} observed plasma lamotrigine concentration in the j^{th} patient; $C_{\text{pred},ij}$ is the corresponding model predicted concentration; and ϵ_{ij} is the residual departure of the observed concentration from the population predicted concentration which was assumed to be a random Gaussian variable with mean of zero and variance σ^2 [19, 20]. The magnitude of residual variability was expressed as a CV.

Regression models

The initial analysis for the population pharmacokinetics of lamotrigine was conducted without including any patient

covariates in the model (BASE 1). Subsequently, univariate analyses for the effect of the covariates body weight (WT), race, age, gender, concurrent therapy with oral contraceptives (OC), dose (mg), and duration of therapy (weeks) on CL_o were modelled as follows:

$$\begin{aligned} TVCL &= \theta_{CL}^{WT1} \cdot WT^{\theta_{CL}^{WT2}} \\ TVCL &= \theta_{CL} \cdot (1 + \theta_{CL}^{RACE} \cdot RACE) \\ TVCL &= \theta_{CL} + \theta_{CL}^{AGE} \cdot AGE \\ TVCL &= \theta_{CL} \cdot (1 + \theta_{CL}^{SEX} \cdot SEX) \\ TVCL &= \theta_{CL} \cdot (1 + \theta_{CL}^{OC} \cdot OC) \\ TVCL &= \theta_{CL} - \theta_{CL}^{DOSE1} \cdot e^{-\theta_{CL}^{DOSE2} \cdot DOSE} \\ TVCL &= \theta_{CL} - \theta_{CL}^{TIME1} \cdot e^{-\theta_{CL}^{TIME2} \cdot TIME} \end{aligned}$$

The effect of non-Caucasians ($RACE=1$) on CL_o was compared with that in Caucasians ($RACE=0$). Oral clearance in females ($SEX=1$) was compared with that in males ($SEX=0$) and CL_o in patients receiving lamotrigine concomitantly with oral contraceptives ($OC=1$) was compared with that in patients receiving lamotrigine alone ($OC=0$). The models for the effect of weight, age, race and gender on V/F were analogous to those for CL_o .

Statistical analysis

For each model, the improvement in the fit obtained on addition of a fixed effect variable into the overall model was assessed by several means. Firstly, the change in the objective function ($\Delta OBJF$) was examined. This change represents a statistic which is proportional to minus twice the log-likelihood of the data and is asymptotically distributed like χ^2 with degrees of freedom equal to the number of parameters added to the model. A change in $OBJF$ of ≥ 7.88 and 10.6 is required to reach statistical significance ($P=0.005$) for the addition of 1 and 2 fixed effects, respectively. In addition, the improvement in the fit by adding a parameter to the model was examined by the precision of the parameter estimate [*i.e.*, % s.e.mean and 95% confidence interval (CI)] and by the reduction in interpatient and residual variability. Examination of the scatterplots of weighted residuals *vs* predicted lamotrigine concentrations was another indicator of the goodness of fit in each model.

Results

Demographic characteristics

The population consisted of 158 Caucasians and 5 Asians of whom 81 were males and 82 females. The population age and weight ranged from 14 to 76 years and 40.5 to 106.5 kg, respectively. Twenty Caucasian females were receiving oral contraceptives. The distribution of body weight and age are shown in Figure 1 and the relationships for body weight and age with other covariates are shown in Figures 2 and 3, respectively. There appears to be slight bimodality in the distribution of age (Figure 1b). Dose ($P=0.002$) and oral contraceptives ($P=0.001$) were significantly correlated with

Figure 1 Frequency distribution of body weight (a) and age (b) in the study population of patients with epilepsy.

age (Figure 2) and body weight for females ($P<0.001$) and Asians ($P=0.0487$) was significantly lower than that in males and Caucasians, respectively (Figure 3). However, the correlation coefficients for the relationships were low ($r<0.3$).

Population pharmacokinetics

Preliminary analysis with the basic pharmacokinetic model showed superiority of the proportional error model ($OBJF = -83.228$) over an additive ($OBJF = 170.160$) and combined model ($OBJF = -83.229$) in estimating residual variability in plasma concentrations of lamotrigine. Thus, the proportional error model was used in all subsequent analyses. Table 1 presents the results from three different models that were examined univariately for the effect of body weight on CL_o and V/F . Oral clearance was slightly but significantly affected by body weight as indicated by the continuous and power models. However, the estimates for the power model were more precise and, therefore, the model was selected for subsequent analyses. None of the models showed a significant effect of body weight on V/F . Results of the univariate analyses with inclusion of other covariates in BASE 1 for CL_o and V/F are presented in Table 2. The largest $\Delta OBJF$ was obtained from the model incorporating the effect of duration of therapy on CL_o and this model was declared as BASE 2, a reference model in the subsequent multivariate analyses with forward elimination. The ranking was followed by the effects of Asians, body weight and females on CL_o . Oral clearance was not significantly influenced by age, oral contraceptives and dose and V/F was unaffected by weight, age, Asians and females.

Figure 2 Bivariate scatterplots showing relationship between age and other covariates. [Gender: 0 = Males, 1 = Females; Race: 0 = Caucasians, 1 = Asians; Oral Contraceptives: 0 = Lamotrigine alone, 1 = Lamotrigine + Oral Contraceptives].

The results of multivariate analyses with forward elimination, incorporating the covariates with significant effects into BASE 2 one by one starting with the effect of Asians on CL_o and continuing along with the rank order established in the univariate analysis, are presented in Table 3. In the presence of an effect of duration of therapy, the effect of Asians on CL_o remained significant, but not that of body weight and females. In a subsequent multivariate analyses with backward elimination the effects of duration of therapy and Asians on CL_o remained significant and, thus, the model was declared optimal for population pharmacokinetics of lamotrigine. Figure 4 compares plots of weighted residuals

vs predicted plasma concentrations of lamotrigine from the basic and final optimal models. Table 4 presents the final population parameter estimates, the interpatient and residual variability and their 95% CI. Each parameter and the corresponding interpatient variability was estimated with good precision, as indicated by the 95% CI of the estimates. The final optimal pharmacokinetic model was used to derive the empirical Bayes estimates of CL_o for individual patients. Figure 5 shows the relationship between individual values of CL_o and duration of therapy, in weeks, with the solid line showing the population estimate from the optimal model.

Figure 3 Bivariate scatterplots showing relationship between body weight and other covariates. [Gender: 0 = Males, 1 = Females; Race: 0 = Caucasians, 1 = Asians; Oral Contraceptives: 0 = Lamotrigine alone, 1 = Lamotrigine + Oral Contraceptives].

Table 1 Summary of univariate analyses evaluating different models for the effect of body weight on oral clearance (CL_o) and apparent volume of distribution (V/F) of lamotrigine.

Effect on	Model	ΔOBF^a	Parameter estimate	95% CI ^b		P value
				lower	upper	
CL_o	$\theta_{CL} + \theta_{CL}^{WT1} \cdot WT^{\theta_{CL}^{WT2}}$ (2 DF)	8.949	$\theta_{CL} = 0.493$ $\theta_{CL}^{WT1} = 0.327$ $\theta_{CL}^{WT2} = 0.376$	-0.473 0.271 0.194	1.459 0.382 0.558	>0.005
	$\theta_{CL} + \theta_{CL}^{WT1} \cdot WT$ (1 DF)	8.569	$\theta_{CL} = 1.49$ $\theta_{CL}^{WT1} = 0.0087$	0.868 -0.0006	2.112 0.0180	<0.005
	$\theta_{CL}^{WT1} \cdot WT^{\theta_{CL}^{WT2}}$ (1 DF)	8.995	$\theta_{CL}^{WT1} = 0.625$ $\theta_{CL}^{WT2} = 0.286$	0.139 0.099	1.111 0.473	<0.005
	$\theta_V + \theta_V^{WT1} \cdot WT^{\theta_V^{WT2}}$ (2 DF)	4.676	$\theta_V = 51.9$ $\theta_V^{WT1} = 0.033$ $\theta_V^{WT2} = 1.58$	11.7 0.028 1.17	92.1 0.038 1.99	>0.005
	$\theta_V + \theta_V^{WT1} \cdot WT$ (1 DF)	4.178	$\theta_V = 2.08$ $\theta_V^{WT1} = 0.573$	1.958 -0.455	2.202 1.601	>0.005
	$\theta_V^{WT1} \cdot WT^{\theta_V^{WT2}}$ (1 DF)	3.737	$\theta_V^{WT1} = 2.08$ $\theta_V^{WT2} = 0.493$	1.959 0.095	2.201 0.891	>0.005

^aReduction in the objective function in comparison to the basic model (BASE 1). A $\Delta OBF \geq 7.9$ and 10.6 is statistically significant for 1 and 2 degrees of freedom (DF), respectively.

^bCI = Confidence interval.

Table 2 Summary of univariate analyses evaluating the effect of other covariates on oral clearance (CL_o) and apparent volume of distribution (V/F) of lamotrigine.

Effect	ΔOBJF^a	Symbol ^b	Parameter estimate	95% CI ^c		P value
				lower	upper	
Age in years on CL _o	4.083	$\theta_{\text{CL}}^{\text{AGE}}$	-0.0038	-0.0095	0.0018	>0.005
Asians on CL _o	10.540	$\theta_{\text{CL}}^{\text{ASIANS}}$	-0.296	-0.414	-0.178	<0.005
Females on CL _o	8.480	$\theta_{\text{CL}}^{\text{FEMALES}}$	-0.098	-0.196	0.000	<0.005
Oral contraceptives (OC) on CL _o	2.945	$\theta_{\text{CL}}^{\text{OC}}$	0.106	-0.064	0.276	>0.005
Dose (mg) on CL _o	7.351	$\theta_{\text{CL}}^{\text{DOSE1}}$	5.39	5.21	5.57	>0.005
		$\theta_{\text{CL}}^{\text{DOSE2}}$	0.0014	-0.0001	0.0029	
Duration of therapy (weeks) on CL _o	37.228 ^d	$\theta_{\text{CL}}^{\text{TIME1}}$	0.335	0.187	0.483	<0.005
		$\theta_{\text{CL}}^{\text{TIME2}}$	0.124	0.034	0.214	
Age in years on V/F	0.098	θ_V^{AGE}	-0.038	-0.552	0.476	>0.005
Asians on V/F	0.023	θ_V^{ASIANS}	3.77	-9.33	16.87	>0.005
Females on V/F	5.338	$\theta_V^{\text{FEMALES}}$	-0.131	-0.325	0.063	>0.005

^aReduction in the objective function in comparison to the basic model (BASE 1). A $\Delta\text{OBJF} \geq 7.9$ and 10.6 is statistically significant ($P \leq 0.005$) for 1 and 2 (duration of therapy and dose) degrees of freedom, respectively.

^bSee Methods for regression models.

^cCI = Confidence interval.

^dThis model was ranked with the highest ΔOBJF and, therefore, was declared as BASE 2 for subsequent multivariate analyses with forward elimination.

Table 3 Summary results of multivariate analyses with forward elimination.

Effect	Symbol	Parameter estimate	95% CI ^a		ΔOBJF^b	Advantage ^c
			lower	upper		
Duration of therapy (weeks) on CL _o (BASE 2)	$\theta_{\text{CL}}^{\text{TIME1}}$	0.335	0.187	0.483	37.228	—
	$\theta_{\text{CL}}^{\text{TIME2}}$	0.124	0.034	0.214		
Asians on CL _o	$\theta_{\text{CL}}^{\text{ASIANS}}$	-0.287	-0.410	-0.164	11.875	Yes ^d
Power of weight on CL _o	$\theta_{\text{CL}}^{\text{WT}}$	0.231	-0.0001	0.463	6.554	No
Females on CL _o	$\theta_{\text{CL}}^{\text{FEMALES}}$	-0.088	-0.179	0.003	7.667	No

^aCI-Confidence interval.

^bReduction in objective function in comparison to preceding model with an advantage.

^cAdvantage on preceding model with significant effect (based on ΔOBJF and 95% CI).

^dThis model which incorporates the effects of duration of therapy (in weeks) and Asians on CL_o was selected as BASE 3 for subsequent multivariate analyses with backward elimination.

Discussion

The present study describes results from an evaluation of the population pharmacokinetics of lamotrigine monotherapy during Phase II/III clinical trials in patients newly diagnosed with epilepsy. No spare blood sampling was scheduled in the study protocols for prospective population pharmacokinetic analysis and, thus, plasma concentrations of lamotrigine collected for drug monitoring, for the purpose of dose adjustment in conjunction with safety and efficacy data, were utilised for retrospective analysis to be incorporated in a regulatory submission. In spite of the limitations of a retrospective analysis, development of a population pharmacokinetic model for lamotrigine allows the estimation of pharmacokinetic parameters (e.g., CL_o and V/F) and the examination of the influence of demographics and other covariates on such parameters, and consequent recommendations for dose adjustment, if needed.

The final population estimate for K_a was 3.18 h⁻¹, producing a population absorption half-life of 0.22 h, a value which is comparable with that obtained in previous formal studies on the pharmacokinetics of lamotrigine in healthy adult males ($\approx 2-5$ h⁻¹). The rapid absorption of lamotrigine is according to its high aqueous solubility. The magnitude of interpatient variability in lamotrigine absorption was inestimable since few plasma concentrations were collected during the absorption phase, attributable to the scheduled late visits to the clinic after drug administration. The effects of the patient covariates on lamotrigine absorption were not examined.

The finding of no age effect on oral clearance and apparent volume of distribution of lamotrigine, using a continuous regression model, is in agreement with results from a formal Phase I study in which the pharmacokinetics of lamotrigine was similar in young and elderly healthy volunteers, where the pharmacokinetics was compared by

Figure 4 Assessment of goodness of fit; Plots of weighted residuals *vs* predicted lamotrigine concentration for the basic (a) and final optimal model (b).

age group [11]. It was not surprising that in our analysis neither CL_o nor V/F were affected by body weight. Previous attempts on results from healthy volunteers failed to reduce the percentage of coefficient of variability when calculating the parameters per kg. Additionally, recent retrospective population analysis on data from an add-on therapy of lamotrigine with other antiepileptic drugs showed no effect of weight on CL_o and V/F (data on file). Hence, patients aged ≥ 14 years might be administered similar doses of lamotrigine irrespective of their body weight, and dose adjustment should be based on the safety and efficacy profiles of the drug as it has been employed in the clinical trials.

The absence of a dose effect on oral clearance clearly indicates linear pharmacokinetics of lamotrigine in patients with epilepsy, such that neither the metabolism of lamotrigine, mostly conjugation, nor its protein binding are affected by the increase in plasma concentrations resulting from the increase in dose. This finding is comparable with data from

formal studies in healthy subjects and patients where dose proportionality in absorption was demonstrated over a wide range of doses [9, 14]. The population analysis also showed similar pharmacokinetics of lamotrigine in males and females. No formal study was designed to examine gender differences in the pharmacokinetics of lamotrigine in healthy volunteers; however, data from six studies in healthy male and female volunteers were combined and subjected to analysis of variance (ANOVA). The results revealed no significant gender differences in the pharmacokinetics of lamotrigine and, thus, confirming the validity of our finding from the population analysis.

The final population estimate of clearance in Caucasian patients after 48 weeks of therapy was 2.28 l h^{-1} , similar to that reported previously ($2.20\text{--}2.52 \text{ l h}^{-1}$) in healthy Caucasian volunteers and patients [9–16]. However, CL_o was 28.7% significantly lower in Asians (1.63 l h^{-1}), similar to the 25% decrease found previously in the population

Table 4 Final estimates of population pharmacokinetic parameters of lamotrigine after oral monotherapy in patients newly diagnosed with epilepsy.

Parameter	Symbol	Unit	Estimated value	95% CI	
				lower	upper
Oral clearance (CL _o)	θ_{CL}	l h ⁻¹	2.28	2.14	2.41
Apparent volume of distribution (V/F)	θ_V	l	77.4	67.4	87.4
First-order absorption rate constant (K _a)	θ_{Ka}	h ⁻¹	3.18	2.31	4.05
Effect of duration of therapy on CL _o	θ_{CL}^{TIME1}	l h ⁻¹	0.338	0.191	0.485
	θ_{CL}^{TIME2}	wk ⁻¹	0.119	0.035	0.203
Effect of Asians on CL _o	θ_{CL}^{ASIANS}	—	-0.287	-0.410	-0.164
CV for interpatient variability in CL _o	ω_{CL}^2	%	32.1	26.6	36.8
CV for interpatient variability in V/F	ω_V^2	%	33.6	13.0	45.7
CV for residual variability	σ^2	%	20.8	18.8	22.6

Structural models:

$$TVCL = \theta_{CL} \cdot (1 + RACE \cdot \theta_{CL}^{ASIANS}) \cdot (1 - \theta_{CL}^{TIME1} \cdot e^{-\theta_{CL}^{TIME2} \cdot TIME})$$

$$TVV = \theta_V$$

$$TVK_a = \theta_{Ka}$$

random effects models:

$$CL_o = TVCL \cdot (1 + \eta_{CL})$$

$$V/F = TVV \cdot (1 + \eta_V)$$

$$K_a = TVK_a$$

$$C_{obs} = C_{pred} \cdot (1 + \varepsilon)$$

where, WT = body weight in kg; race is 0 and 1 for Caucasians and Asians, respectively; TVCL = Typical population value for CL_o; TVV = Typical population value for V/F; TVK_a = Typical population value for K_a.

Figure 5 Relationship between final NONMEM empirical Bayes estimates of oral clearance and duration of lamotrigine monotherapy. ○ empirical Bayes estimate, — population model.

pharmacokinetic analysis of lamotrigine as an add-on therapy where 53 non-Caucasians were included in the analysis (data on file) compared with five patients in our analysis. Although the findings are similar, the 28.7% lower clearance in Asians should be interpreted cautiously due to the small number of patients used in our analysis. Lamotrigine oral clearance increased from the first dose by 17% over the 48 weeks duration of therapy, from 1.94 to 2.28 l h⁻¹ in

Caucasians, as presented in Figure 5. The latter reflects a combination of dose related auto-induction which is complete within 2 weeks and the longer period of dose escalation from 50 mg once daily dosing in the first week ending with up to three times a day dosing of 200 mg from week 24 onward. This 17% increase in CL_o will be automatically accommodated in an escalation therapy scheme. The final magnitude of interpatient variability in

CL_o was 32.1%, probably mostly related to interindividual variability in the metabolism rate of lamotrigine, mainly conjugation.

The final population estimate for apparent volume of distribution was 77.4 l, or 1.14 l kg^{-1} based on mean population body weight of 68 kg, and as mentioned earlier it was unaffected by weight, race, gender and age. This estimate is similar to the average value of 1.2 l kg^{-1} reported in healthy young volunteers [9–12] but 37% lower than the population estimate of 1.8 l kg^{-1} in patients treated with various enzyme-inducing antiepileptic drugs (data on file). The final magnitude of interpatient variability in V/F was 33.6%.

Consequent to the significant effects of race and duration of therapy on oral clearance of lamotrigine and no effect on V/F , elimination half-life was also affected by these covariates. Thus, the population estimate of half-life in Asians was 40% longer than in Caucasian. Also, due to auto-induction in clearance, half-life was reduced by 14.8% during the 48 weeks of therapy, from 27.6 to 23.5 h in Caucasians and 38.7 to 33.0 h in Asians. These population estimates are similar to the mean half-life reported in healthy volunteers and patients (range: 23–37 h) receiving lamotrigine monotherapy [9–16]. Bearing in mind the likely errors in these estimates, any alterations in dosing frequency required as a result of the half-life considerations may be easily accommodated by once or twice daily dosing.

The population estimate of residual variability was modest at 20.8%. This represents a composite of model misspecification, assay variability, intraindividual variability and patient non-compliance. Some of this variability may be related to assumptions made in constructing the database for NONMEM where dosing intervals were assumed to be exactly 24, 12, and 8 h for the once, twice, and three times a day dosing regimen, respectively.

In conclusion, the population pharmacokinetic parameter estimates of oral clearance and apparent volume of distribution after lamotrigine monotherapy were generally in good agreement with findings from formal studies in healthy subjects and patients. Steady-state plasma concentrations of lamotrigine will be slightly affected by the modest significant effects of race and auto-induction on clearance, but in view of the wide therapeutic margin of lamotrigine and 21% residual variability, no dosage adjustment is warranted.

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