PHARMACOMETRIC ANALYSES OF LAMOTRIGINE IN SPECIAL POPULATIONS: APPLICATION TO PREGNANT WOMEN, YOUNGER ADULT AND ELDERLY EPILEPSY PATIENTS

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DEDICATION

To my parents and sisters for their love, and belief in me

&

To the memory of K. Sanjeeva Reddy and K. Sujatha Reddy

ABSTRACT

The pharmacokinetics (PK) of lamotrigine (LTG) is understudied in pregnant women and elderly patients with epilepsy. Both pregnancy and advanced age are expected to result in changes in the LTG PK, which may cause potential loss of efficacy or safety. Optimal dosing of LTG in these special populations requires characterization of PK and its variability among the individuals. This dissertation work aimed at characterizing gestational age-associated changes in LTG PK and seizure control and age-related changes in LTG PK, and exploration of potential benefits of a newly developed LTG formulation over the conventional form in the elderly. The long-term goal of this research work is to create evidence-based guidelines for dosing LTG in both pregnant women and elderly patients with epilepsy.

The change in apparent clearance (CL/F) of LTG was quantified with respect to gestational age and postpartum weeks in pregnant women who were maintained on LTG alone or with non-interacting drugs. During pregnancy, we identified two subpopulations of women that exhibited different rates of increase in LTG CL/F. The gestational age-associated increase in CL/F displayed a ten-fold higher rate in subpopulation I (0.120 L/h/week) compared to subpopulation II (0.0115 L/h/week). Such drastic changes in CL/F would require frequent dosage adjustments in subpopulation I. Further investigations revealed heterogeneity in the racial mix between the two subpopulations with a larger prevalence of whites (80%) in subpopulation I than in subpopulation II. We anticipate that race-associated genotypic variations in the activity or induction of UGT1A4 or polymorphisms in estrogen receptors could partly explain the varying degrees of enhanced CL/F between the two groups of pregnant women and may warrant further investigation. In the postpartum period, we calculated that an average duration of 3 weeks is required for LTG CL/F to reach preconception values, and that clinicians may need to taper the dose of LTG to the baseline prescribed dose within that time interval. When exploring seizure frequencies in pregnant women, the seizure rate was low most likely due to effective therapeutic drug monitoring. Future studies with a larger number of patients may provide information on exposure-response and time course changes of seizures in pregnant women.

With the creation of a novel stable-labeled intravenous LTG formulation we were able to administer LTG by two routes (i.e., oral and intravenous) simultaneously in younger adults and elderly patients with epilepsy. We also demonstrated a comparable bioequivalence between extended-release and immediate release formulations in terms of steady-state area under the concentration-time curve, trough and average steady-state plasma concentration in elderly patients with epilepsy. We found a comparable absolute bioavailability (75%) of LTG tablets in both younger adult and elderly patients. However, the LTG clearance (CL) was 27% lower on average for elderly patients compared to younger adults. We hypothesize the observed reduction in CL may be caused by a reduced enzyme capacity (or UGT1A4 expression) and/or liver volume in the elderly group. Therefore, we recommend future studies to investigate age-selective differences in UGT1A4 expression.

Overall, the studies presented in this thesis characterized the LTG PK in special populations that are underrepresented in clinical studies. We were unable to fully explain some of the PK findings in pregnant women or the elderly due to the lack of information on UGT1A4 genotypes. Therefore, future studies of LTG in these populations should investigate genotypic variations and expression of the main metabolic enzyme UGT1A4.

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CHAPTER 1

INTRODUCTION

1.1 EPILEPSY

Epilepsy is a common neurological disorder, with a worldwide prevalence of 1% (1). It is defined by the International League against Epilepsy and the International Bureau for Epilepsy as “a disorder of the brain that is characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure (2)”. Approximately100,000 new cases per year are reported in the United States (3). The incidence of epilepsy reaches a plateau in adult years and gradually increases after 54 years of age, reaching highest level in the oldest age group (1). The seizures of 70% of epilepsy patients can be managed with available medications (4); however, 20 to 30% of patients do not respond to medical or surgical treatment (5). In case of treatment failure with a particular antiepileptic drug (AED), patients may be managed with another AED or a combination of AEDs. Patients who do not respond to AEDs may undergo surgery or vagal nerve stimulation (5). Table 1.1 lists the AEDs that are commercially available in the United States. Older AEDs are associated with a narrow therapeutic index, more side effects, and significant between-subject variability in pharmacokinetics (PK). Newer AEDs are believed to possess better efficacy and safety profiles compared to the older AEDs. The use of newer AEDs has extended beyond the treatment of epilepsy and have emerged to treat bipolar disorder, migraine, mood disorders, and neuropathic pain (Table 1.1).

1.2 LAMOTRIGINE (LTG): INDICATION AND EFFICACY

LTG, 3,5-diamino-6(2,3-dichlorophenyl)-1,2,4-triazine (Figure 1.1), is structurally unrelated to other AEDs (6). It was developed initially as an antifolate compound at Galxo Wellcome but was screened on animal models of epilepsy. It was first approved in Ireland in 1990 and in the UK in 1991 and subsequently approved by the US FDA in 1994. It is approved for adjunctive therapy of partial seizures, primary generalized tonic-clonic seizures, generalized seizures for Lennox-Gastaut syndrome in adult and paediatric patients aged ≥ 2 years, for conversion to monotherapy in patients aged ≥ 16 years with partial seizures, and for maintenance therapy of bipolar I disorder in adults aged ≥ 18

years (7). LTG's efficacy is comparable to carbamazepine (8,9) but has been shown to have a better tolerability and provides higher quality of life measure in epilepsy patients (8–10).

1.2.1 Mechanism of Action

The precise mechanism of action of LTG in humans is not well established (11); however, it is hypothesized to act on sodium channels and, possibly, on other ion channels (12–15). *In vitro* pharmacological studies suggest that LTG inhibits voltage-sensitive sodium channels, and consequently modulates the release of excitatory amino acids such as glutamate and aspartate (7).

1.2.2 Clinical pharmacokinetics

The immediate release oral formulation of LTG is rapidly and completely absorbed following oral administration with negligible first-pass metabolism and near complete bioavailability in healthy volunteers. LTG reaches peak plasma concentration in 1.3 – 4.7 hours (7). The absolute bioavailability of the LTG gelatin capsule formulation is 98% in normal healthy volunteers relative to intravenous LTG isethionate (16). The first order absorption rate constant (k_a) for LTG ranges from 0.38 to 3.57 h^{-1} (17–20).

Studies conducted in healthy volunteers and patients report a LTG apparent volume of distribution (V/F) between 77 to 132 L (16,17,19–25). LTG is moderately protein bound (55%) (17) indicating a low potential for displacement interactions. LTG's apparent clearance (CL/F) has been reported in studies of both healthy volunteers and patients with epilepsy to be 1.96 to 2.64 L/h (16–30). LTG exhibits first-order linear PK that could be well described by a one-compartment model (31). In the literature, LTG PK is adequately described by a one-compartment model with first order absorption and elimination (16–28).

LTG is a low clearance drug that is almost completely metabolized by N-glucuronidation, a conjugative pathway that is thought to not be significantly affected by age (32,33). The human hepatic enzyme UGT1A4 (34–36) is mainly responsible for the conversion of LTG to LTG N-glucuronide, but other enzymes such as UGT1A3 (34) and UGT2B7 (35)

may also be involved. Approximately 70% of LTG's total oral dose is recovered in the urine, 90% of which is in the form of glucuronide metabolites (17). The remaining10% is recovered as an unchanged LTG (17). Metabolites excreted in urine are 2-N glucuronide (major), 5-N glucoronide (minor), N-2 methyl LTG (minor), and reminder being unidentified (37,38). None of these metabolites are pharmacologically active.

LTG has a relatively long elimination half-life (23-37 h) (16,17,23–25,28–30). The half-life is approximately 24 hours under steady-state conditions (7). Coadministration of enzyme-inducing AEDs such as phenytoin, carbamazepine, primidone and phenobarbital reduce the mean LTG half-life to 12.6-14.4 hours (7,29). In contrast, concomitant administration of enzyme-inhibiting AED such as valproate significantly increases the half-life of LTG to 48.3-70.3 hours (7,29).

Autoinduction of LTG metabolism is controversial in the literature. Studies that included healthy volunteers (17) and elderly epilepsy patients (21) did not show autoinduction. However, a population analysis of epilepsy patients (n=163; 14-76 years) did show a modest autoinduction, which is completed within 2 weeks of LTG therapy (20). With the autoinduction, a 17% increase in CL/F and a 15% reduction in half-life were reported (20).

1.3 LTG FORMULATIONS

Various LTG branded formulations such as immediate release (Lamictal®), extended-release (Lamictal® XR™), chewable dispersible (Lamictal®) and orally disintegrating (Lamictal® ODT™) tablets in different strengths are commercially available.

LTG immediate release (LTG-IR) formulation is well studied in the literature for PK and safety. With no concomitant enzyme-inducing or inhibiting agents, LTG-IR results in PK profiles with an average trough-to-peak concentration ratio of 0.75 (39). In general, extended-release formulations reduce peak-to-trough fluctuation, and may have an improved adverse effect profile in comparison to immediate release formulations (39).

The LTG extended-release (LTG-XR) formulation (Glaxo SmithKline) was approved by the US FDA in 2009 for patients ≥ 13 years of age. LTG-XR enteric-coated tablets are

formulated by a modified release eroding matrix core (DiffCORE^{TM}) that reduces the dissolution rate of LTG compared to LTG-IR and prolongs the drug release over approximately 12 – 15 hours (40). Recently, steady-state PK of LTG-XR compared to LTG-IR have been studied in subjects with epilepsy in an open-label crossover study (41). In a neutral metabolism group (no concomitant inducers or inhibitors), steady-state peak concentration values in serum are on average 11% lower (geometric mean: 6.83 *vs.* 7.82 µg.h/mL), and the peak-to-trough fluctuation is reduced by 37% (geometric mean: 0.34 *vs.* 0.55). Further, time to reach peak concentration (Tmax) is extended from 1.5 hour to 6 hour after switching from LTG-IR to LTG-XR (41).

1.4 LTG IN THE ELDERLY

The incidence of epilepsy is higher in the elderly than in younger adults (1). As per United States Census, the number of people ≥ 65 years of age is projected to increase by 135% between 2000 and 2050. During the same timeframe, people ≥ 85 years of age, who are susceptible to various comorbidities and who will most likely need long-term health care services, are projected to increase by 350% (42). Therefore, there will be more elderly epilepsy patients by 2050.

Pharmacokinetics may alter with age (32,43). Age-related physiological changes in the elderly may affect drug disposition characteristics such as absorption, distribution, metabolism and elimination (32,44–46). Table 1.2 presents physiological changes that occur with age and their potential effect on drug pharmacokinetics (32,46). In addition, elderly patients receive a wide variety of medications due to the presence of multiple comorbidities, which further complicates drug disposition and increases the likelihood of drug-drug interactions. Due to the changes in pharmacokinetics and the complications that arise when treating elderly patients (i.e., drug-drug interactions) it is very important to study drug pharmacokinetics within this vulnerable population in order to improve dosing strategies.

LTG is well tolerated in older patients with epilepsy (47) and has a low potential for drug-drug interactions compared to other AEDs which undergo metabolism through cytochrome P450 enzyme system. These characteristics make LTG a good candidate for

treating elderly patients. However, there is limited pharmacokinetic information in elderly patients. A limited number of studies investigated the effect of age on LTG pharmacokinetics (19–22,26). Only two studies compared the PK characteristics between younger and older populations (24,48) however, the effect of age on LTG pharmacokinetics is still not clear in the literature. Posner et al., compared LTG pharmacokinetics of elderly healthy volunteers (n=12; mean age 71 years [range: 65 - 76 years]) with younger healthy volunteers (n=12; mean age 31 years [range: 26 – 38 years]) (24). Following a single 150 mg oral dose, the peak concentration (2.31 vs 1.82 µg/mL) and the area under the concentration curve (91.8 vs 56.6 µg.h/mL) were increased by 27% and 55% in the elderly group, respectively. The mean elimination half-life ($t_{1/2}$) (31.2 h [range: 24.5 – 43.4 h]) was 6.3 hours longer and the mean CL/F (0.40 ml/min/kg [range: 0.26 – 0.48 ml/min/kg]) was decreased by 37% in the elderly group (24). Another study comparing young *vs.* older adult outpatients receiving LTG monotherapy found that the CL/F was 20% lower in older patients (48). In contrast, two separate population pharmacokinetic studies showed no age effect on CL/F; however, few elderly subjects were included in the analyses (20,22). Moreover, a population pharmacokinetic study in elderly epilepsy patients (n=148; mean age 70.6 years [range: 59 – 92 years]) reported CL/F that is not different when compared to the CL/F in adult population (21).

1.5 LTG IN PREGNANT WOMEN

Women suffering from chronic diseases such as asthma, diabetes mellitus, hypertension, epilepsy, depression and other mood disorders continue taking their medication during pregnancy. It is well known that the physiological changes due to pregnancy can influence drug absorption, distribution, metabolism, and elimination (Table 1.3) (49–53). These pharmacokinetic changes may lead to a potential loss of efficacy and/or safety of the drug. Nevertheless, for many drugs, there is little or no information available about such changes at different stages of pregnancy.

In the United States, approximately 1.1 million women with epilepsy are of childbearing age with an average birth rate of 20,000 babies per year (54). It has been demonstrated that the average risk of seizure frequency increases by 15% to 25% during the course of

pregnancy (55). Seizures due to epilepsy during pregnancy may have severe consequences for both the mother, and the developing fetus. Unlike other drugs, withdrawal of AEDs during pregnancy is therefore usually not reasonable.

In recent years, LTG has became a primary choice to treat epilepsy and bipolar I disorder in pregnant women due to low risk of teratogenic complications (2-4.5%) compared to other AEDs (56–59). A population-based observational study in the UK shows that the prevalence of LTG prescribing in female adolescents (12-18 years) is increased by 10 fold between 1993 and 2006 as opposed to decreased prescribing trends for carbamazepine and valproate (60). As per the US FDA approval, LTG is a Pregnancy Category C drug (i.e., known adverse effect on fetus in animal reproduction studies but no adequate information and well-controlled studies in humans). It is recommended for use during pregnancy; however, the trade-offs between potential benefits and potential risks involved with the therapy should be taken into account (7,40).

Several studies report a 19 to 75% increase in seizure frequency in patients treated with LTG during pregnancy compared to the frequency prior to or after pregnancy (55,61–63). The increase in seizures is thought to be due to decrease in LTG blood levels during the course of pregnancy (61–70). The rising levels of sex hormones during pregnancy may induce the UDP-glucuronosyltransferases (UGTs) (71) and consequently increase the metabolism of LTG. Previous studies in pregnant women demonstrate that LTG CL/F increases 65-197%, 93-236%, and 88-250% in the first, second and third trimesters, respectively (61,64,65,67,68) and rapidly declines to preconception values within 2-4 weeks post delivery (61,63,64,67–69). The increase in LTG CL/F during pregnancy is more pronounced than other AEDs which are metabolized by cytochrome P450 enzyme system (72). Current clinical practice includes therapeutic drug monitoring of LTG by measuring in the plasma/serum levels at regular intervals during pregnancy.

1.6 DETERMINATION OF PHARMACOKINETICS UNDER STEADY-STATE CONDITIONS: STABLE ISOTOPE METHODOLOGY

Epilepsy patients are commonly on a continuous AED therapy; interruption of therapy would expose patients to an increased risk of seizures. The use of stable isotope enabled

AEDs provides a method to rigorously characterize pharmacokinetics and bioavailability in patients under steady-state conditions without disrupting the maintenance therapy. The stable isotope methodology has been successfully utilized in pharmacokinetic and bioavailability studies of various AEDs such as phenytoin (73), carbamazepine (74), and valproic acid (75,76).

Availability of analytical instruments with improved selectivity and sensitivity to detect and measure a molecular entity has made the simultaneous measurement of stable labeled and non-labeled compounds in biological fluids more practical. The measurement of a stable isotope tracer compound with analysis by gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-mass spectrometry (LC-MS) is an elegant method for pharmacokinetic and bioavailability studies (77). For example, in a bioavailability study, a stable isotope labeled drug can be administered by one route (e.g. intravenous) and the non-labeled drug by a test route (e.g. oral) at the same time, and plasma levels of both forms of the drug can be measured simultaneously on a GC-MS or a LC-MS. Therefore, this methodology reduces the number of blood samples, as well the amount of time and money associated with drug analysis.

Use of stable isotope methodology for pharmacokinetic and bioavailability studies assumes that the introduction of a stable isotope into a molecular structure does not alter drug kinetics. However, it is important to note that labeling of a drug by deuterium may alter the drug kinetics due to a potential isotope effect upon oxidative metabolism. In contrast, compounds that are labeled with ^{13}C and ^{15}N and undergoing conjugative metabolism would not exhibit a change in their pharmacokinetics (78).

1.7 PHARMACOMETRICS

Pharmacometrics is an emerging science that is commonly applied in the field of clinical pharmacology. In general, pharmacometrics is the science of quantitative pharmacology and is commonly used to build pharmaco-statistical models to describe drug pharmacokinetics and exposure-response (pharmacokinetic-pharmacodynamic; PK-PD) relationships.

1.7.1 Population analysis

The term “population analysis” refers to the building of a pharmaco-statistical model to describe concentration-time or exposure-response data obtained from a population of interest following administration of a pharmacological agent. The advantage of this analysis is that one can evaluate the sources and correlates of variability in drug pharmacokinetics or pharmacodynamics among a population of interest. It does not require intensive sampling and/or response data from an individual. The process borrows information from all the individuals present in the analysis cohort and characterizes drug pharmacokinetics and/or pharmacodynamic characteristics. Therefore, population analysis is very useful in special populations (e.g., pregnant women, pediatrics, elderly patients etc.,) in which intensive sampling is not feasible. Moreover, this approach has great applicability in sparse sampling scenarios such as seen with therapeutic drug monitoring (79–81). With these advantages, the “population analysis” is widely accepted, as evidenced by the amount of published research over the last three decades following the introduction of the nonlinear mixed effect method by Sheiner and Beal (82).

1.7.2 Population model

A population model defines two levels (hierarchies) of random errors (effects) to describe the parameter variability. At the first level, error arises from the individual level (e.g., concentrations or pharmacodynamic responses from individuals) and the model describing the error at the individual level can be written as:

$$Y_{ij} = f(x_{ij}, \Theta_i) + \varepsilon_{ij}$$

Y_{ij} is the j^{th} observation in the i^{th} individual, and f is a specified function of the structural model according to independent variables x_{ij} (e.g., time and dose). $\mathbf{\Theta_i}$ represents a vector of structural parameters for the i^{th} subject and ε_{ij} is the j^{th} residual error (random unexplained variability) in the i^{th} subject. The first level of the random error, ε_{ij}, represents a composite of model misspecification, assay variability, intraindividual variability, and process error (79), and follows a distribution with mean 0 and variance σ^2. At the second level, error occurs at the population level due to variation of structural

parameters between the individuals (interindividual variability). The interindividual variability can generally be written as:

$$\Theta_i = g(V_i, \theta) + \eta_i$$

g is a function that defines the covariate model of the parameters, and $\boldsymbol{V}_i$ represents the i^{th} individual's vector of covariates; θ is the typical value for the parameters representing the fixed effects. η_i represents the interindividual variability of the parameters for the i^{th} individual and follows a distribution with mean of 0 and variance-covariance matrix of **Ω** (79,81,83).

1.7.3 Important estimation methods

The statistical principle of maximum likelihood estimation is employed in population analysis. Because of the nonlinear nature of the population PK-PD models, the nonlinear mixed effect method employs a linearization approximation to compute the likelihood function. The first order (FO) approximation method is a simple approximation method where both random error models are linearized around $\eta = 0$ and $\varepsilon = 0$ based on first-order Taylor series expansion (84). The first-order conditional estimation (FOCE) method is next level of estimation method, which uses first-order Taylor series expansion about individual's empirical Bayes estimates of interindividual random effect (η_i) rather than about zero (85,86). The Laplace estimation method is more exact method than FOCE and FO. This method also approximates the first order Taylor series expansion around individual conditional estimates (η_i) but includes a hessian matrix (second order derivatives) rather than approximating it with a function of gradient vector as in the case of FO and FOCE methods (85).

1.7.4 Count data modeling

Count is a discrete variable and the count data describe the number of times of an event occurred in a particular interval of time. In drug development programs, count data are obtained when events such as seizure counts, angina episodes, panic attacks, etc., are observed in a clinical study. Modeling of count data to establish exposure-response

relationship requires understanding of distributions that describe discrete variables. Among those discrete distributions, the Poisson (PS) distribution is widely used to model various pharmacodynamic count responses (87–95). However, a PS model assumes that the mean of counts is equal to the variance of the counts. In addition, it also assumes that the observed counts in two distinct time intervals are independent. These assumptions violate zero inflation (many occurrences of zero counts), overdispersion phenomena (variance > mean) and Markovian feature (past occurrence of an event influence the future occurrence), if any, observed in a study. These issues are generally handled by alternative distribution assumptions or by incorporating zero inflation parameter or Markovian elements in the model. For accounting overdispersion, Negative Binomial (NB) distribution is generally assumed. Zero-inflated data can be well described by zero-inflated PS or zero-inflated NB models (88,90). More details on these models are presented in methods section of Chapter 3: Modeling of seizure counts following lamotrigine therapy in pregnant women.

1.8 RESEARCH OBJECTIVES

The overall objective of this research work was to provide pharmacokinetic information on LTG in order to provide more informed dosing in special populations. The populations explored were pregnant women, younger adult and elderly epilepsy patients. Studies in the pregnant women aimed at investigating gestational age-associated changes in LTG pharmacokinetics and seizure control. In the elderly patients, we attempted to investigate age-related changes in LTG pharmacokinetics and explored the potential benefits of a newly developed LTG formulation over the conventional form. Thus, the specific aims of this thesis were:

1. To quantify the changes in LTG CL/F in pregnant women with respect to gestational age, and to account for the clinical characteristics that may influence the CL/F. In addition, the aim of this research work was to propose a dosing strategy for pregnant women with epilepsy or bipolar I disorder.

2. To characterize the time course changes of seizure frequency in pregnant women with respect to gestational age and to investigate the relationship between LTG exposure and seizure control.

3. To investigate the effect of advancing age on LTG clearance and bioavailability and to explore the effect of patient specific covariates such as body weight and sex on LTG pharmacokinetics. Intravenous stable labeled LTG allowed the estimation of absolute bioavailability and the exploration of the age effect on LTG clearance while excluding variability in absorption.

4. To characterize the pharmacokinetics of LTG in elderly patients with epilepsy using a stable isotope methodology and to explore the potential benefits of LTG extended-release formulation in comparison to immediate release formulation.

The findings related to aims 1 and 2 are presented in Chapters 2 and 3, respectively. The results pertaining to aims 3 and 4 are described in Chapters 4 and 5, respectively.

Table 3.1. Commercially available AEDs in the United States.

AED	Partial	Generalized	Other Seizures	Status Epilepticus	Other Indications
Older AEDs					
Carbamazepine	+	+	Mixed		Trigeminal neuralgia
Clonazepam		+	LGS		Panic disorder
Clorazepate	+		-		Anxiety disorders
Diazepam			-	+	Anxiety disorder
Ethosuximide		+	-		-
Phenobarbital	+	+	-	+	Insomnia
Phenytoin	+	+	-		-
Primidone	+	+	-		-
Valproic acid	+	+	Multiple		-
Newer AEDs					
Felbamate	+		LGS		-
Gabapentin	+		-		Postherpetic neuralgia
Lamotrigine	+		LGS		Bipolar I disorder
Lacosamide	+		-		-
Levetiracetam	+	+	-		-
Oxcarbazepine	+		-		-
Pregabalin	+		-		Neuropathic pain; Postherpetic neuralgia
Rufinamide			LGS		-
Tiagabine	+		-		-
Topiramate	+	+	LGS		Migraine; Obesity
Zonisamide	+		-		-
Vigabatrin	+		Infantile spasms		-

AED: Antiepileptic drug; LGS: Lennox-Gastaut syndrome

Table 1.2. Age-related physiological changes and their effect on drug pharmacokinetics (32,46).

Physiological changes in elderly	**Potential pharmacokinetic changes**
↓ Intestinal motility	Drug absorption and bioavailability
↑ Body fat	↑ V_d (for lipophilic drugs)
↓ Total body water	↓ V_d (for hydrophilic drugs)
↓ Serum albumin	↑ f_u, ↑ V_d
↓ Blood flow to liver, liver function	↓ CL
↓ Renal blood flow and glomerular filtration rate	↓ CL_r
↓ Phase I metabolism	↓ CL_m
↔ Phase II metabolism	↔ CL_m

↔: no change; ↑: increase/up regulated; ↓: decrease/down regulated; V_d: volume of distribution; f_u: unbound fraction; CL: clearance; CL_r: renal clearance; CL_m: metabolic clearance

Table 1.3. Physiological changes during pregnancy and their effect on drug pharmacokinetics (49–53).

Physiological changes during pregnancy		**Potential pharmacokinetic changes**
↑	gastric pH, gastric emptying time and gastrointestinal transit time	Drug absorption and bioavailability
↑	Total body weight and body fat	↑ V_d (for lipophilic drugs)
↑	Extra cellular fluid, total body water and plasma volume	↑ V_d (for hydrophilic drugs)
↓	Serum albumin	↑ f_u, ↑ V_d
↑	Blood flow to liver and kidney	↑ CL
↑	Renal blood flow and glomerular filtration rate	↑ CL_r
	Change in hepatic enzyme activity e.g.,	
↑	CYP3A4, 2D6, 2C9, 2A6,	↑ CL_m
↑	UGT1A4, 2B7	
↓	CYP1A2, 2C19	↓ CL_m

↑: increase/up regulated; ↓: decrease/down regulated; V_d: volume of distribution; f_u: unbound fraction; CL: clearance; CL_r: renal clearance; CL_m: metabolic clearance

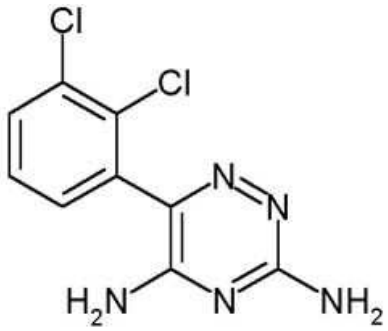

Figure 1.1. Chemical structure of Lamotrigine

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CHAPTER 2

A MODEL-BASED CHARACTERIZATION OF CHANGES IN LAMOTRIGINE CLEARANCE DURING PREGNANCY

2.1 INTRODUCTION

Epilepsy is a common neurological disorder in pregnant women and requires continuous treatment with antiepileptic drugs (AEDs) to protect the mother and the developing fetus. In recent years, lamotrigine (LTG) has became a primary choice to treat epilepsy and bipolar disorder in pregnant women (1,2) partly due to low risk of teratogenic complications (2-4.5%) compared to other antiepileptic drugs (3–6). However, LTG pharmacokinetics (PK) undergoes marked changes during pregnancy (7–16) and if a women remains on her prepregnancy LTG dose seizure frequency will increase (8,11,17). There are no concrete guidelines for dosage management of LTG during pregnancy and the early postpartum period. Standard practice includes frequent monitoring of LTG levels by clinicians in order to adjust doses throughout pregnancy. The susceptibility of the developing fetus should be kept in mind when managing AED therapy.

LTG is a moderately protein bound (55%) (18) and has a relatively long half-life (23-37 h) (18–25). It is mainly (>90%) metabolized by UGT1A4 (26–28) and to a lesser extent by UGT1A3 (26) and UGT2B7 (27). The rising levels of sex hormones during pregnancy may induce UDP-glucuronosyltransferases (UGTs) (29) and consequently increase the metabolism of LTG. Previous studies demonstrate that LTG oral clearance (CL/F) increases up to 250% during pregnancy (7–9,13,14) and rapidly declines to preconception values within 2-4 weeks post delivery (7,8,12–15). The increase in LTG CL/F during pregnancy is more pronounced than those AEDs metabolized by cytochrome P450 enzyme system (30).

Although several small studies demonstrated changes in LTG CL/F during gestation (7–16), a systematic analysis was not performed to demonstrate the time related changes of CL/F and its variability throughout pregnancy. Thus, the objective of our study was to quantify the CL/F time course changes during and after pregnancy and to account for the clinical characteristics that may influence the CL/F.

2.2 METHODS

2.2.1 Study population

Subjects were women ≥17 years of age on a LTG regimen for the treatment of epilepsy or bipolar disorder. Only women who were pregnant or planning pregnancy were enrolled in a prospective observational study to investigate time course changes of PK in AEDs during pregnancy (Emory Women's Epilepsy and Mental Health Programs). The inclusion criteria for this study were LTG monotherapy or LTG with other medications that were not likely to affect LTG disposition; and willing to continue LTG therapy during pregnancy. Those with significant medical issues (uncontrolled thyroid disease, severe anemia, kidney or liver dysfunction or progressive cerebral disease), those taking alcohol or recreational drugs, those with a history of medication nonadherence, those unable to keep daily seizure diaries personally or with the help of a caregiver, and those with active suicidal ideations were excluded from the study. Women were screened between December 2002 and August 2006 for enrollment in the study. The study was approved by Institutional Review Board of Emory University School of Medicine. Patients were informed of the study and written consent was obtained from each woman before enrollment.

2.2.2 Study design

Subjects were enrolled at different stages of pregnancy such as preconception, trimesters 1 through 3, and the first postpartum year. Use of other medications, missed LTG doses and the number and types of seizures for women with epilepsy were recorded via seizure-medication diaries. A neurologic examination and review of subject seizure-medication diary were done at each visit. In addition, intervening illnesses and maternal or newborn complications, if any, were recorded. At each visit, body weight (BWT), body mass index (BMI), age, and gestational age (GA) in weeks were carefully recorded. One maternal blood sample was collected at each neurology office visit and occasionally at obstetrics offices. Thus, the LTG concentrations in plasma were not trough levels. Doses were adjusted on an individual basis depending on an individual's determined prepregnancy LTG levels. Subjects received their adjusted individual therapeutic oral LTG daily doses

(50-1400 mg) as once daily or divided doses during different stages of pregnancy. The majority of subjects were on a twice-a-day dosing schedule. Subject medical records maintained by the treating obstetrician, the delivery hospital, and the treating pediatrician were obtained for review. The delivery date of each subject was recorded and accordingly, postpartum weeks (PPW) were calculated.

2.2.3 LTG bioanalysis

Blood was centrifuged at 2,750 rpm at 3°C for 10 minutes, and 600 µL aliquots of plasma were transferred to polypropylene tubes. The plasma samples were frozen at -80°C until analysis. LTG plasma concentrations were measured using a validated assay (31) employing high performance liquid chromatography with ultraviolet detection (Chromsystems, GmbH, Munich, Germany). The lower and upper limit of quantification of the bioanalytical assay was 0.25 µg/mL and 20 µg/mL, respectively. The intra-assay and inter-assay coefficient of variations were <5%. Samples were pooled and assayed in batches.

2.2.4 Population PK modeling

A population PK analysis was performed using a qualified installation of nonlinear mixed-effects modeling software, NONMEM version 7 (ICON Development Solutions, Ellicott City, MD, USA) with a GNU Fortran 95 compiler on a Dell Precision 470 workstation (Dell, Round Rock, TX, USA) with Windows XP x64 Professional edition (Microsoft, Redwood, WA, USA). Diagnostics plots were constructed using the R statistics software (version 2.11.1) (32). The first-order conditional estimation method with η-ε interaction (FOCE-INT) was employed for all model runs.

LTG exhibits first-order linear PK that could be well described by a one compartmental model (33). However, due to the relatively long elimination half-life of LTG (23-37 h) (18–25) compared to dosing intervals, a steady-state infusion model (Equation 1) was assumed (34). Since the visits were separated by at least one week, it was assumed that the steady-state conditions had been attained before the next visit. According to the steady-state infusion model, the observed concentration (C_{obs}) is equal to the average

steady-state concentration ($C_{ss, avg}$) of LTG and is related to the LTG dose rate (daily dose divided by 24 h) through a regression parameter, CL/F*, as shown in equation 1. The CL/F* approximates the true CL/F as $C_{obs} \approx C_{ss, avg}$. This assumption is reasonable with LTG due to its long half-life. The CL/F* has a clinically relevant meaning since it approximates CL/F, an important parameter for dose adjustments in therapeutic drug monitoring (TDM). For purpose of clarity, the CL/F* will be referred to as CL/F in the remainder of the chapter.

$$C_{obs} = \frac{DoseRate}{CL/F^*} \qquad (1)$$

Interindividual variability (IIV) was modeled using an exponential error model (Equation 2). θ_i is the parameter estimate for the i^{th} individual, $TV\theta$ is the typical value of the parameter in the population, $\eta^{\theta i}$ are individual-specific random effects for the i^{th} individual and assumed to be normally distributed with mean 0 and variance ω^2. This assumption imparts a log-normal distribution on the parameter of interest and expresses the variability as a coefficient of variation (CV).

$$\theta_i = TV\theta \times \exp(\eta^{\theta i}) \qquad (2)$$

Residual unexplained variability (RUV) was characterized by a proportional error model (Equation 3). C_{ij} is the j^{th} observed concentration of i^{th} individual, $\hat{C}_{ij}$ is the j^{th} model predicted concentration based on the individual parameters for i^{th} individual. ε_{ij} is the proportional error component of RUV, for the j^{th} measurement in the i^{th} individual and is assumed to be normally distributed with mean 0 and variance σ^2.

$$C_{ij} = \hat{C}_{ij} \times (1 + \varepsilon_{ij}) \qquad (3)$$

2.2.5 Covariate modeling

Primary modeling efforts were focused on characterizing the time course changes in LTG PK during pregnancy. Both linear and nonlinear (E_{max}) models were considered for investigating the effect of GA and PPW on CL/F^* during pregnancy and in postpartum weeks, respectively. The effect of other covariates on CL/F was guided by graphical

approaches. Missing values of time dependant covariates (BWT, BMI) within a patient, if any, were linearly interpolated using within-subject recorded values from remaining visits. Model discrimination was assessed by a likelihood ratio test comparing objective function values (OFVs). An OFV difference (ΔOFV) of 3.84 was considered to be significant ($\chi^2, p < 0.05$) when two nested models with a difference of one parameter (df = 1)) were compared. The Akaike's information criterion (AIC) was used to compare non-nested models. Additionally, model development was guided by various goodness-of-fit criteria, including diagnostic scatter plots, plausibility of parameter estimates, precision of parameter estimates and by our knowledge of physiological changes in pregnancy.

2.2.6 Model evaluation

A nonparametric bootstrap procedure (35) was employed for model evaluation. One thousand data sets were generated by random sampling with replacement from the original data set using PDx-Pop 4.1 (ICON Development Solutions, Ellicott City, MD, USA). Population parameters were estimated for each bootstrap data set using the final model. The bootstrap results were pooled only from the runs with successful convergence and covariance steps. The 2.5th, 50th and 97.5th percentiles of the parameter distributions were computed and compared with the results from the NONMEM final model.

In addition, the final model was qualified by examining standardized visual predictive check (SVPC) plots (36). The final model parameter estimates were used to simulate 1000 replicates of the original dataset. A percentile ($P_{i,j}$) for the jth observation of the ith individual was calculated (Equation 4) from the marginal distribution of the model-simulated concentrations as a function of GA. $Ind_{ij,n}$, an indicator variable, equals 1 if jth observed concentration of ith individual is greater than the nth model-simulated concentration of that individual at jth time, and equals 0 otherwise. The $P_{i,j}$ were then plotted against GA to construct the SVPC.

$$P_{i,j} = \frac{1}{1000}\sum_{n=1}^{1000} Ind_{ij,n} \qquad (4)$$

2.3 RESULTS

2.3.1 Study population characteristics

Sixty-nine women (56 whites, 10 blacks and 3 Asians) met the inclusion criteria. Baseline characteristics of the subjects are presented in Table 2.1. A total of 613 plasma concentrations were collected at routine clinic visits before, during, and after pregnancy. Distribution of the time of observations during the course of pregnancy is presented in Table 2.2. Of the 613 observations, 399 samples were drawn during pregnancy and 214 samples before or after pregnancy. A single blood sample was obtained from 45 women during delivery. Seven observations were excluded from the analysis because of missing dose information.

2.3.2 Model building

The steady-state infusion model adequately described the maternal plasma concentration data. The baseline CL/F (CL_{BL}; 2.15 L/h) was primarily estimated from the preconception concentration data with a CV of 40.6%. The influence of pregnancy on CL/F was described by GA and PPW during pregnancy and the postpartum period, respectively. During pregnancy, the change in CL/F was best described with GA as a covariate in a linear function with a constant slope parameter. Visual inspection of the plots of *post hoc* LTG CL/F versus GA revealed a separation of two trends of increasing LTG CL/F during pregnancy. Therefore, we tested for the possibility that a fraction of our pregnant women belong to a subpopulation with a significantly lower rate of enhanced CL/F via the implementation of mixture models in NONMEM (37). The mixture model indicated that majority (72%) of our population had a rate of 0.12 L/h increase in their CL/F per week, while 28% of pregnant women displayed a slower rate of increase (0.0115 L/h) for each week of gestation. Inclusion of this mixture model resulted in a significant drop in the OFV ($\Delta OFV=13$, $p<0.01$), reduced the intersubject variability on the rates of enhanced CL/F by 77% compared to a model that lacks mixture effect and accounted for the observed trends of GA-associated increase in LTG CL/F (Figure 2.1). After accounting for the mixture model, the remaining between subject variability was estimated to be 42.2%.

The CL/F change from baseline value at delivery (ΔCL_{DEL}) was predicted for those individuals with no observation during delivery using the individual's empirical Bayes estimate (EBE) of the slope. The change in CL/F after delivery was described by PPW as a covariate in an exponential function with a first-order rate constant (k). Based on this model, the derived half-life (0.693/k) of the decline in the enhanced CL/F from baseline at delivery (ΔCL_{DEL}) was 0.55 weeks, indicating that the oral CL of LTG is expected to return to baseline values within 3 weeks of delivery. Due to the presence of sparse data in the postpartum period, estimation of the interindividual variability on k was not possible; consequently the variance of eta for k had to be fixed to zero. After taking into account the effects of both GA and PPW, the remaining unexplained variability was 46%. The final model equations to estimate the LTG CL/F during preconception, pregnancy, and postpartum are presented in Table 2.3. The simultaneous fitting of these model equations provided an adequate description of the data and resulted in physiologically meaningful parameter estimates with considerable precision.

2.3.3 Covariate analysis

The relationship between other clinical covariates and CL/F was examined by eta or delta plots (CL minus TVCL). The diagnostic plots had demonstrated the evidence of no effect of age, BWT, BMI and race on CL/F during different stages of pregnancy. Nonetheless, the possible relationship between CL/F and BWT was statistically evaluated; the inclusion of the BWT did not improve the model. Therefore, except the influence of pregnancy (GA and PPW as covariates) no other covariate described the changes of CL/F during pregnancy and postpartum. Furthermore, there was no significant association between the presented covariates and the CL_{BL}.

2.3.4 Model evaluation

Diagnostic plots for different stages of pregnancy revealed that the final model was consistent with the observed data (Figure 2.2). Plots of conditional weighted residuals (CWRES) were generally well scattered across the range of predicted concentrations (Figure 2.3) and GA (Figure 2.4) with most of the data being within 3 units from the zero-ordinate indicating no overall systemic bias in the model diagnostics. Final model

parameter estimates and bootstrap confidence intervals are presented in Table 2.4. The estimated model parameters were within 13% of the medians obtained from the bootstrap procedure. Furthermore, the 95% CI of parameters from NONMEM were comparable to bootstrap 2.5^{th} and 97.5^{th} percentiles. Thus, the model evaluation indicates the accuracy and precision of parameter estimates as well as the stability of the final model.

The SVPC plot for the final model that characterized LTG CL/F during the course of pregnancy is shown in Figure 2.5. From the plot, it was observed that the $P_{i,j}$ values for the observed LTG concentrations were in general uniformly well distributed between 0 and 1. Approximately 10.6% of $P_{i,j}$ values were outside the 5^{th} and 95^{th} percentiles. This result suggests that the data have been reasonably well described by the PK model with good predictive performance.

2.4 DISCUSSION

The major result of this analysis of LTG oral CL in pregnant women with epilepsy is that the CL/F of LTG was significantly influenced by gestational age (GA) and postpartum weeks (PPW). In addition, the CL model identified two subpopulations of pregnant women in which LTG CL/F increased linearly at rates of 0.12 and 0.0115 L/hr for each week of GA during pregnancy, and declined exponentially with a common rate constant of 1.27 per week after delivery. After accounting for these effects, LTG CL/F was not affected by age, race, BWT or BMI. Our results suggest that both GA and PPW are the main determinants of LTG doses throughout pregnancy and after delivery.

We characterized the changes in LTG oral CL during the course of pregnancy and in postpartum weeks. A unique feature of our analysis is the modeling of both GA and PPW as continuous covariates. This approach is more clinically relevant and statistically powerful than accounting for the effect of these covariates in a categorical manner. From a physiological standpoint, LTG CL/F is expected to gradually change over time rather than displaying sudden variations over trimesters. Overall, the model predicted a linear increase in LTG CL/F during pregnancy and a nonlinear exponential decline in CL/F after delivery.

Interestingly, our model identified two subpopulations of pregnant women that exhibited different rates of increase in LTG CL/F during pregnancy (Figure 2.1). The first population included a majority of the pregnant women (72%) and displayed a ten-fold higher rate of increase in LTG CL/F per week than the second population. The estimated rate of increase in LTG CL/F for population I (0.12 L/hr per week) predicts 67%, 156% and 223% increases of CL/F from baseline, while that of population II (0.0115 L/hr per week) confers lower degrees of elevation in LTG oral CL (6.4%, 15%, and 21.4%) by the end of conventional first (12 weeks), second (28 weeks) and third (40 weeks) trimesters, respectively. These findings are of clinical importance as they indicate that varying degrees of change in LTG CL/F are expected during gestation where some patient populations would display a dramatic increase in their oral CL compared to others. For instance, an average woman from population I would need approximately 22% increase in her LTG dose at week 4 of gestation when such an adjustment of dose would be required only at the end of the third trimester for a woman from population II. Therefore, we anticipate the population of pregnant women with a faster increase in their CL/F to require more frequent dosage adjustments, display greater variability in LTG concentrations, and gain more benefits from TDM during pregnancy than those with a slower change in LTG oral CL over the weeks of gestation. It is worth mentioning that our estimated changes in LTG CL/F during pregnancy are in general in agreement with previous studies of pregnant women that reported increases of 65-197%, 93-236%, and 88-250% in baseline LTG CL/F for the first, second, and third trimesters, respectively (7–9,13,14).

With the exception of race, none of the subjects characteristics, including weight, BMI, and age, were found to differ between the identified subpopulations. Women of Caucasian race were identified to have a faster increase in CL/F about 80% of the time, while black races were equally distributed between the two subpopulations. Racial associated genotypic variations in the activity or induction of UGT1A4 could partly explain the varying degrees of enhanced oral CL between the two groups of pregnant women and may warrant further investigations (14,38–40). Indeed, Pennell et al, reported a higher unbound CL/F rates in white than black women ($p = 0.031$) maintained on LTG

therapy during pregnancy (8). Similarly, we found a mean reduction in the effect of GA in black versus white women, but the effect did not achieve statistical significance.

In the postpartum weeks, the increased LTG CL/F from baseline declined at an exponential manner with an estimated rate constant (k) of 1.27 per week. The calculated half-life (0.693/k) of the decline in the enhanced CL/F from baseline at delivery (ΔCL_{DEL}) was 0.55 weeks, which means that LTG oral CL is expected to reach the baseline value within 3 weeks after delivery. Clinicians may therefore need to taper the dose of LTG to the baseline prescribed dose within 3 weeks of delivery. Similar to our finding, previous clinical trials determined a postpartum period of 2-4 weeks for LTG CL/F to reach preconception values in pregnant women receiving LTG as a monotherapy or in combination with other antiepileptic agents (7,8,12–15).

Covariate analysis results from our study failed to detect any effects for body size measurements (BWT and BMI) or age on LTG oral CL at baseline (CL_{BL}), during pregnancy, and after delivery. The lack of a BWT effect on CL/F could be attributed to the narrow range of included baseline weight (51-95 kg), and the fact that our model did not account for potential confounders such as polymorphic UGT1A4 (38,41–44) and hormonal changes in pregnant women. Furthermore, it is possible that the strong collinearity between weight and GA had turned the residual effect of BWT on LTG CL/F to be insignificant after accounting for the GA associated changes in oral CL. In a study of pregnant women maintained on LTG monotherapy, Pennell et al, found the changes of LTG oral CL during pregnancy and childbirth to be independent of body weight (13). In contrast, previous PK studies of LTG in patient populations other than pregnant women identified weight as a significant covariate on LTG CL/F but mostly included wider ranges of BWT than were represented in our study (45–49). Regarding age, our results remain consistent with the Pennell et al's study who found the age of pregnant women to have no significant effect on LTG oral CL (8). The population of our study consisted of young pregnant women of narrower age range (17 to 42 years) than the average human life span. This may explain the lack of an age effect on LTG CL/F.

The standard diagnostic plots and bootstrap confidence intervals suggest that the final steady state infusion model was adequate and precise in describing both baseline and changes of LTG oral CL in pregnant women. The standardized visual predictive check (SVPC) plot indicates that the final model adequately described the PK data with good predictive performance. The population mean of baseline CL/F (CL_{BL} = 2.15 L/h) is in close agreement with those reported (1.96 – 2.64 L/h) from other traditional (18–25) and population PK studies (45–51). Furthermore, the magnitude of the between-subject variability in both the baseline CL/F (43%) and rates of enhanced oral CL (45%) during pregnancy are consistent with previous reports that noted a substantial interindividual variability in CL/F rates during pregnancy (8,30). The remaining residual variability (46%) could partly be attributed to a model misspecification since we modeled C_{ss} through CL/F^{*}.

In conclusion, we characterized the changes of LTG CL/F during the course of pregnancy and after delivery using a population PK-based approach. Varying degrees of increase in CL/F was observed during pregnancy and is likely attributed to racial differences in the inducibility or activation of the metabolizing enzymes. Pregnant women with a faster rate of enhanced CL/F may need frequent dosage adjustment and closer monitoring than those with a lower rate of increase in their oral CL. Further studies are needed to identify the underlying reason for varying rates of enhanced CL/F during pregnancy and would benefit from investigating the polymorphisms involved in the regulation and expression of UGT1A4 or induction-related estrogen receptors. Following childbirth, CL/F rapidly reached preconception values within 3 weeks. Thus, LTG doses should be tapered to preconception doses within 3 weeks of delivery. The satisfactory performance of the oral CL model may justify its applicability in dosing pregnant women on LTG monotherapy and those who receive LTG with no interacting medications.

Table 4.1. Summary of subject demographics

Baseline characteristics	**Mean ± SD or number**
No. of subjects	69
Age (in years)	31.1 ± 5.4
Body weight (in lbs)	154.9 ± 33.4
Height (in inches)	64.9 ± 2.5
BMI (in kg/m^2)	26.4 ± 5.7
Race	
Whites	56
Blacks	10
Asians	3

BMI: Body mass index

Table 2.2. Distribution of concentrations and time dependent changes in covariates (mean ± SD) with respect to gestational age

Characteristic	PC (GA < wk 0)	TM1 (~ 0 ≤ GA < 15 wks)	TM2 (~ 15 ≤ GA < 28 wks)	TM3 (~ 28 ≤ GA < 44 wks)	PP (~ 33 ≤ GA < 92 wks)
No. of subjects	13	39	47	60	55
No. of concentrations	35	88	140	171	179
Body weight (in lbs)	148.7 ± 28.0	144.6 ± 25.5	157.2 ± 27.1	171.9 ± 28.0	156.9 ± 31.2
BMI (in kg/m^2)	25.9 ± 4.2	24.3 ± 4.2	27.1 ± 5.4	29.1 ± 5.0	26.5 ± 5.5

PC: preconception; TM: trimester; PP: postpartum; GA: Gestational age; BMI: Body mass index

Table 2.3. Final model equations

Stage	Model equation	Description
Preconception	$CL/F = CL_{BL}$	CL_{BL}: baseline CL/F
Pregnant	Population I: $CL/F = CL_{BL} + Slope_1 \times GA$ Population II: $CL/F = CL_{BL} + Slope_2 \times GA$	GA: gestational age Slope: rate of change of CL/F
Postpartum	$CL/F = \Delta CL_{DEL} \times \exp(- k \times PPW) + CL_{BL}$	ΔCL_{DEL}: CL/F change from baseline, at delivery; k: first-order rate constant; PPW: postpartum weeks

Table 2.4. Final model parameter estimates

Stage of Pregnancy	Parameter	Estimate (%RSE) [95% CI]	Bootstrap median [2.5th, 97.5th percentile]
Preconception	CL_{BL} (L/h)	2.15 (6.4) [1.88, 2.42]	2.13 [1.90, 2.46]
	$\omega^2_{CL/F}$	0.165 (34.4) [0.054, 0.276]	0.161 [0.055, 0.274]
	IIV for CL_{BL}, %CV	40.6 [23.2, 52.5]	40.1 [23.4, 52.3]
Pregnant	$Slope_1$ (L/h/wk)	0.120 (11.4) [0.093, 0.147]	0.119 [0.023, 0.153]
	$Slope_2$ (L/h/wk)	0.0115 (49.5) [0.00035, 0.023]	0.0113 [0.0039, 0.106]
	Mixture probability (Population II)	0.277 (28.7) [0.121, 0.433]	0.285 [0.139, 0.593]
	ω^2_{slope}	0.178 (38.0) [0.045, 0.311]	0.158 [0.038, 0.298]
	IIV for slope, %CV	42.2 [21.2, 55.8]	39.7 [19.5, 55.6]
Postpartum	k (1/wk)	1.27 (10.3) [1.01, 1.53]	1.28 [1.10, 4.64]
	σ^2	0.210 (11.9) [0.161, 0.259]	0.207 [0.165, 0.257]
	RUV, proportional, %CV	45.8 [40.1, 50.9]	45.5 [40.6, 50.7]

IIV: interindividual variability; RUV: random unexplained variability: % CV: percent coefficient of variation; %RSE: percent relative standard error; CI: confidence interval

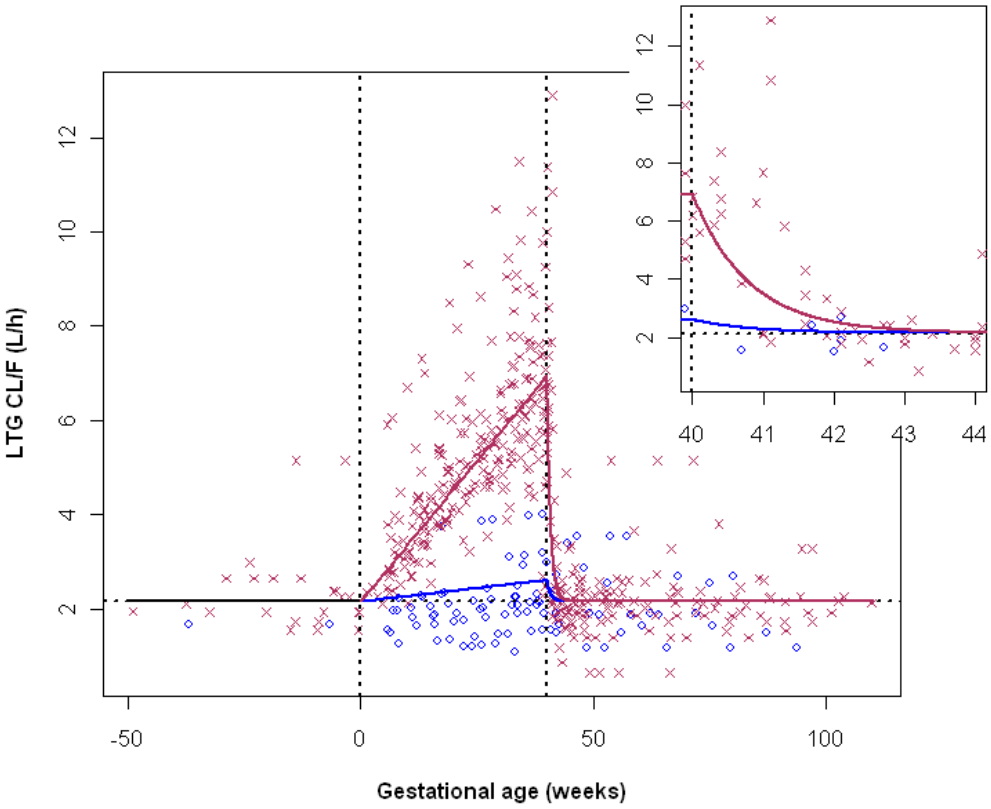

Figure 2.1. *Post hoc* estimates of LTG CL/F during different stages of pregnancy. Maroon and blue data points indicate the *post hoc* CL/F estimates for subjects with high rate of increase (population I) and low rate of increase (population II) in CL/F during pregnancy, respectively. Solid lines through the data indicate population predicted CL/F profiles. Vertical dashed lines at gestational age 0 and 40 weeks separate stages of pregnancy (< 0 weeks: preconception; 0-40 weeks: pregnant; >40 weeks: postpartum). Inset plot displaying the data and population model predictions of first 4 postpartum weeks. Horizontal dashed line in the plot represents baseline CL/F (2.15 L/h).

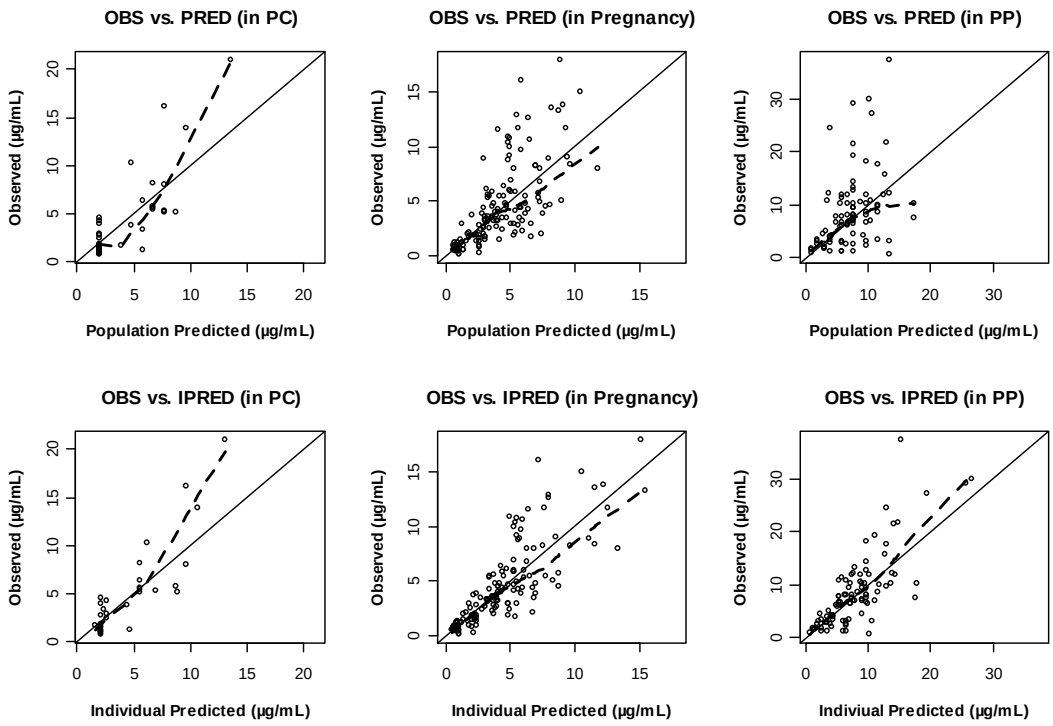

Figure 2.2. Observed *vs.* population predicted (PRED) and observed *vs*. individual predicted (IPRED) LTG plasma concentrations, by stage of pregnancy (PC: preconception; PP: postpartum). Data points indicate the observed *vs.* predicted LTG plasma concentrations. Solid straight line passing through origin is a line of identity and dashed line is a smooth for observed *vs.* predicted concentrations.

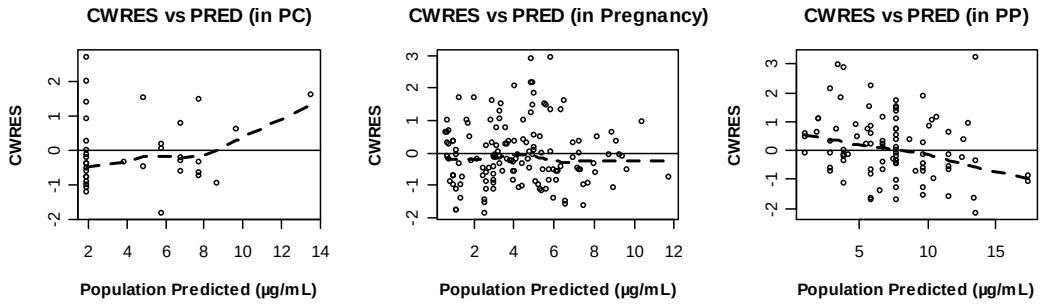

Figure 2.3. Conditional weighted residuals (CWRES) *vs.* population predicted (PRED) LTG plasma concentrations, by stage of pregnancy (PC: preconception; PP: postpartum). A solid line (y=0) is included as a reference for CWRES. Dashed line is a smooth for CWRES *vs.* PRED concentrations.

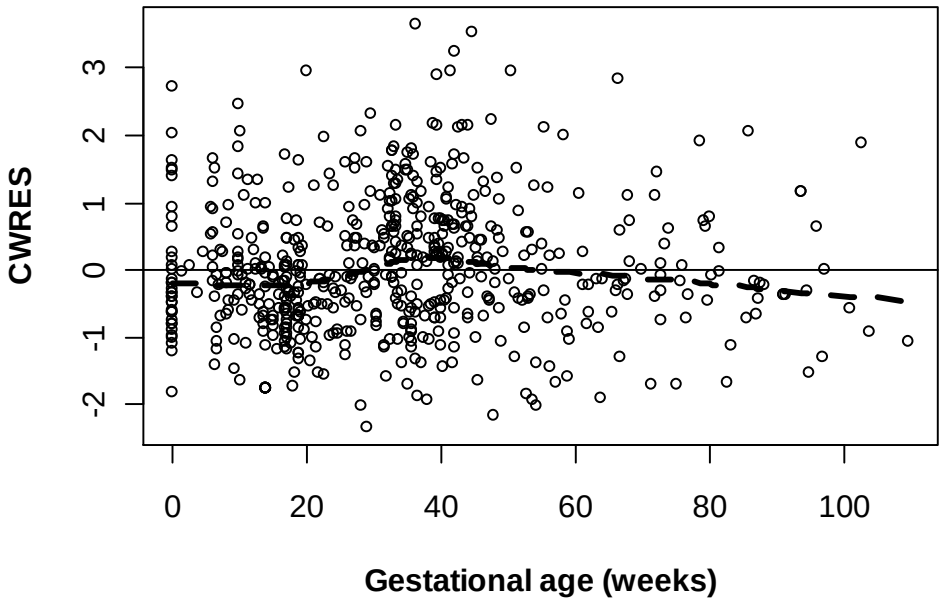

Figure 2.4. Conditional weighted residuals (CWRES) *vs.* gestational age. A solid line (Y=0) is included as a reference for CWRES. Black dashed line is a smooth for CWRES *vs.* gestational age (GA).

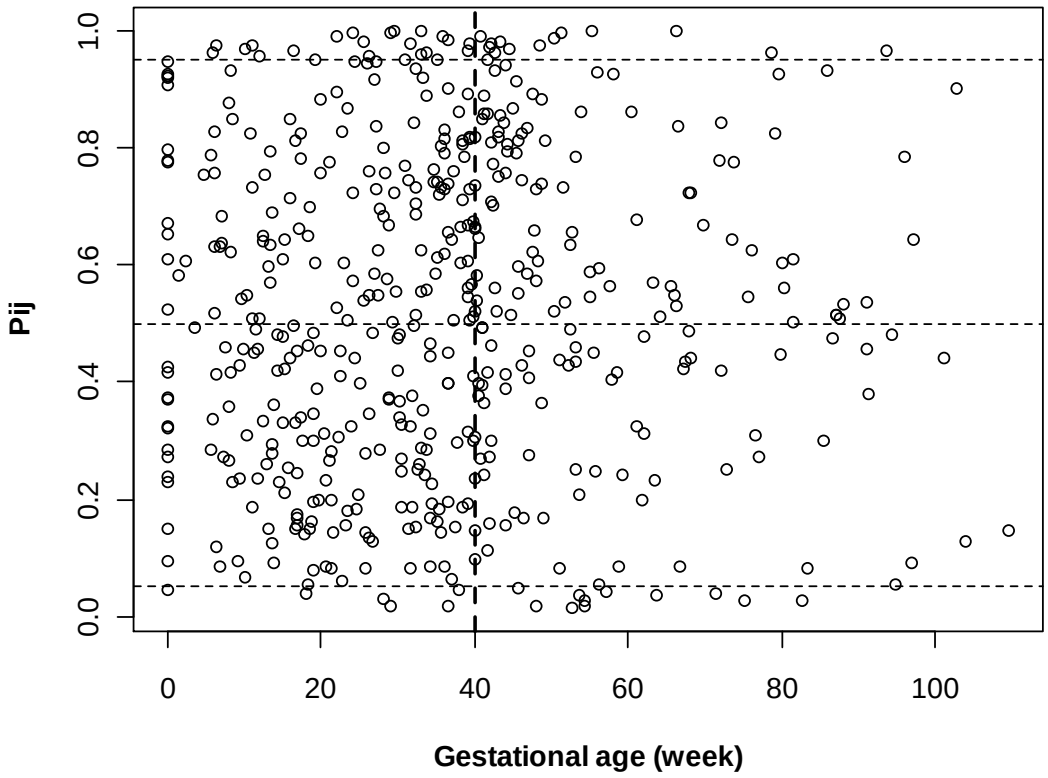

Figure 2.5. Standardized visual predictive check (SVPC) plot for the final model that characterized LTG CL/F during the course of pregnancy. P_{ij}, a percentile for the j^{th} observation of the i^{th} individual calculated from the marginal distribution of the model-simulated concentrations. Open circles, calculated $P_{i,j}$ values; dashed lines, 5^{th}, 50^{th}, and 95^{th} percentiles (from bottom to top). Vertical bold dashed line at 40 weeks represents approximate time of delivery (0 weeks: preconception; 0-40 weeks: pregnant; >40 weeks: postpartum).

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CHAPTER 3

MODELING OF SEIZURE COUNTS FOLLOWING LAMOTRIGINE THERAPY IN PREGNANT WOMEN WITH EPILEPSY

3.1 INTRODUCTION

“An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in brain” (1). The seizures increase by 15-25% during pregnancy in women with epilepsy (2). The increase in seizure frequency can be attributed to a number of altered pharmacokinetic and non-pharmacokinetic factors during pregnancy (3). Seizures during pregnancy may be harmful to the mother and the developing fetus. Therefore, careful monitoring of medications is important when treating epilepsy in pregnant women.

Lamotrigine (LTG) has emerged as a drug of choice to treat epilepsy in pregnant women due to low risk of teratogenic complications (2-4.5%) compared to other antiepileptic drugs (4–7). Several studies report a 19 to 75% increase in seizure frequency in patients treated with LTG during pregnancy (2,10–12). The increase in seizures is thought to be due to decrease of LTG blood levels during the course of pregnancy (10–19).

Seizure count is a discrete response variable. In the literature, several studies modeled seizure counts by a nonlinear mixed-effects modeling approach (20–29). This approach facilitates investigation of possible covariates to explain the variability among the population, and most importantly to characterize exposure-response relationships and time course changes in seizure counts.

The primary objective of this seizure count data analysis was to develop a pharmacodynamic (PD) count model that could be subsequently linked to the pharmacokinetic (PK) model developed for the LTG concentration data in Chapter 2, and to characterize the time course changes of seizure counts in pregnant women with respect to gestational age.

3.2 METHODS

The study was approved by Institutional Review Board of Emory University School of Medicine. Written informed consent was obtained from each woman before the data was collected.

3.2.1 Study population

Subjects were women ≥17 years of age on a LTG regimen for the treatment of epilepsy or bipolar disorder. Only women who were pregnant or planning pregnancy were enrolled in a prospective observational study to investigate time course changes of pharmacokinetics in AEDs during pregnancy (Emory Women's Epilepsy and Mental Health Programs). The inclusion criteria were LTG monotherapy or LTG with other medications that were not likely to affect LTG disposition; and willingness to continue LTG therapy during pregnancy. Those with significant medical issues (uncontrolled thyroid disease, severe anemia, kidney or liver dysfunction, or progressive cerebral disease), those taking alcohol or recreational drugs, those with a history of medication nonadherence, those unable to keep daily seizure diaries personally or with the help of a caregiver, and those with active suicidal ideations were excluded from the study. Women were screened between December 2002 and August 2006 for enrollment in the study.

3.2.2 Study design

Subjects were enrolled at different stages of pregnancy such as preconception, trimesters 1 through 3, and the first postpartum year. Individual seizure-medication diaries were maintained for women with epilepsy to record the number of seizures, types of seizures, other medications and missed LTG doses. A neurologic examination and review of subject seizure-medication diaries were done at each visit. In addition, intervening illnesses and maternal or newborn complications, if any, were recorded. At each visit, body weight (BWT), body mass index (BMI), age and gestational age (GA) in weeks were carefully recorded. Doses were adjusted on an individual basis depending on an individual's LTG levels and clinical response. Subjects received their adjusted individual therapeutic oral LTG daily doses (50-1400 mg) as once daily or divided doses during different stages of pregnancy. The majority of subjects were on a twice-a-day dosing schedule. Subject medical records maintained by the treating obstetrician, the delivery hospital, and the treating pediatrician were obtained for review. The delivery date of each subject was recorded and accordingly, postpartum weeks (PPW) were calculated.

3.2.3 Seizure count data analysis

A mixed effects modeling approach was performed. A qualified installation of nonlinear mixed-effects modeling software, NONMEM version 7 (ICON Development Solutions, Ellicott City, MD, USA) with a GNU Fortran 95 compiler on a Dell Precision 470 workstation (Dell, Round Rock, TX, USA) with Windows XP x64 Professional edition (Microsoft, Redwood, WA, USA) was used for the data analysis. The Laplacian conditional estimation method with likelihood option was employed for all model runs. Diagnostic plots were constructed using the R statistics software (version 2.11.1) (30).

Exploratory data analysis was performed to identify underlying characteristics of the data. Accordingly, appropriate modeling assumptions were considered. Various distribution models with different characteristics in terms of zero inflation, overdispersion, Markovian (MAK) features, and mixture probability were fit to the data. The following distribution models were implemented in NONMEM and compared to select a suitable model that best describes the data.

3.2.3.1 Poisson (PS) model

A PS process is a stochastic process which counts number of occurrences of an event in a particular interval of time. Each count in the process occurs at random in distinct intervals of time and the random variable associated with the counts follows a PS distribution. The PS process is memoryless as the probability of occurrence of an event is not influenced by the previous numbers of occurrences of that event.

The PS model is the simplest distributional model to analyze count data and is predominantly used to analyze various pharmacodynamic count responses (20,22–29). It has only one parameter, λ, which is defined as the mean value of counts in a specified time interval. A major assumption of the PS model is that the λ is assumed to be equal to the variance of the counts. In addition, it also assumes that the observed counts in two distinct time intervals are independent.

In the current analysis, the PS model (Equation 1) was considered as a starting point to describe the seizure count data obtained from pregnant women. Equation 1 represents the

PS model. Y_{ij} is the observed seizure count of the i[th] subject on the j[th] time interval, λ_i is the mean seizure count per week (mean seizure rate) for the i[th] individual. $P(Y_{ij} = n)$ is the conditional probability when the Y_{ij} observation equals n counts. $n!$ represents the factorial of the n counts. The $n!$ is approximated by the Stirling's formula (22) as shown in equations 2a and 2b. The Stirling's formula includes an extra term for the approximation of low numbers of n (last term in equation 2b).

$$P(Y_{ij} = n) = \frac{\lambda_i^n}{n!} \times e^{-\lambda_i} \quad \text{for } n = 0, 1, 2, 3,\ldots \qquad (1)$$

$$n! = 1 \quad \text{for n =0} \qquad (2a)$$

$$n! = \sqrt{2\pi} \times n^{\left(n+\frac{1}{2}\right)} \times e^{-n} \times \left(1 + \frac{1}{12n}\right) \quad \text{for n>0} \qquad (2b)$$

3.2.3.2 Zero-Inflated Poisson (ZIP) model

A high frequency of zero counts in specified time intervals during observational period of a study results in zero-inflated data. This type of data can be modeled by the a ZIP model (22,24). The ZIP distributional model is a combination of a Bernoulli and a Poisson distribution. The ZIP model enables the determination of a probability of observing zero counts. Equations 3a and 3b represent the ZIP model. ρ_i is the parameter that determines the probability of observing zero seizures in the i[th] individual. The probability is determined by summing up the probabilities of zero seizures that resulted from susceptible ($[1- \rho_i]e^{-\lambda i}$) and non-susceptible ($\rho_i$) states (24). All other terms in equations 3a and 3b have same meaning as in the PS model.

$$P(Y_{ij} = 0) = \rho_i + (1 - \rho_i)e^{-\lambda_i} \qquad (3a)$$

$$P(Y_{ij} = n) = (1 - \rho_i) \times \frac{\lambda_i^n}{n!} \times e^{-\lambda_i} \quad \text{for } n = 1, 2, 3,\ldots \qquad (3b)$$

3.2.3.3 Hurdle (HDL) model

A HDL model is a truncated version of the PS model (24). Similar to the ZIP model, it determines the probability of observing zero counts with one minor difference. The parameter, ρ_i, in the HDL model is simply the probability of observing zero seizures in the ith individual irrespective of the state (24). Equations 4a and 4b represent the HDL distributional model. All other terms in equation 4b have same meaning as in the PS model.

$$P(Y_{ij} = 0) = \rho_i \qquad (4a)$$

$$P(Y_{ij} = n) = (1-\rho_i) \times \frac{\lambda_i^n}{n!} \times e^{-\lambda_i} \times (1-e^{-\lambda_i})^{-1} \text{ for } n = 1, 2, 3,\ldots \qquad (4b)$$

3.2.3.4 Negative Binomial (NB) model

Oftentimes, clinical count data exhibit a phenomenon called overdispersion, where the variance of the counts exceeds the mean of the counts. The overdispersion phenomenon is generally described using NB distributional assumptions (21,22). In addition to the λ_i, the NB model includes a parameter, ψ_i, which describes the degree of overdispersion of seizure counts in the ith individual. Equation 5 corresponds to the NB distributional model. λ_i has the same meaning as described in the PS model.

$$P(Y_{ij} = n) = \left(\frac{\Gamma\left(n + \frac{1}{\psi_i}\right)}{n! \times \Gamma\left(\frac{1}{\psi_i}\right)} \right) \times \left(\frac{1}{1+\psi_i \times \lambda_i} \right)^{\frac{1}{\psi_i}} \times \left(\frac{\lambda_i}{\frac{1}{\psi_i} + \lambda_i} \right)^n \quad \text{for } n = 0, 1, 2, 3,\ldots \quad (5)$$

Where $\Gamma(x)$ is the gamma function, i.e. $\Gamma(x) = (x\text{-}1)!$, which is also approximated by the Stirling's formula as shown in equations 2a and 2b.

3.2.3.5 Zero-Inflated Negative Binomial (ZINB) model

A count data with high frequency of zeros and overdispersion phenomena can be modeled using a ZINB model. Equations 6a and 6b describe the ZINB distributional model. The parameters ρ_i and ψ_i have the same meaning as in the ZIP and the NB model, respectively. Since the model includes both ρ_i and ψ_i, it handles both zero inflation and overdispersion to describe seizure count data (22).

$$P(Y_{ij} = 0) = \rho_i + (1-\rho_i) \times \left(\frac{1}{1+\psi_i \times \lambda_i} \right)^{\frac{1}{\psi_i}} \quad (6a)$$

$$P(Y_{ij} = n) = (1-\rho_i) \times \left(\frac{\Gamma\left(n + \frac{1}{\psi_i}\right)}{n! \times \Gamma\left(\frac{1}{\psi_i}\right)} \right) \times \left(\frac{1}{1+\psi_i \times \lambda_i} \right)^{\frac{1}{\psi_i}} \times \left(\frac{\lambda_i}{\frac{1}{\psi_i} + \lambda_i} \right)^{n} \quad \text{for } n > 0 \quad (6b)$$

3.2.4 Modeling the Markovian (MAK) characteristics

Many PD variables show a certain degree of interdependency between neighboring observations, a feature that could be modeled incorporating MAK features. In the current analysis, only first-order MAK characteristics were modeled in order to explore if there was any influence of previous visit seizures on the current visit seizures. A covariate PDV was created in the dataset to explore the MAK characteristics. The PDV was coded as 0 or 1 if the previous visit was without or with seizures, respectively. The distributional model equations were written separately for the scenarios PDV=0 and PDV=1, and accordingly, the parameters were estimated (22). Therefore, the number of parameters is doubled with a first order MAK model compared to a model without MAK feature.

3.2.5 Model building

The parameters λ and ρ were modeled using a log-linear canonical link function (Equation 7) and a logit link function (Equation 8), respectively. Since the time intervals for seizure observations were not uniform or not of the same length across the study duration within each subject, a time offset log(TDUR) was included in the log-linear canonical link function (Equation 7). TDUR represents the time during which seizure counts were recorded. The anti-natural logarithm of estimate θ_λ was calculated and interpreted as a population estimate of the mean weekly seizure count (λ). The anti-natural logarithm of estimate $\theta\rho$ was used to calculate ρ. In the HDL model, the parameter ρ was interpreted as a population estimate for the probability of observing zero seizures whereas in the ZIP model both λ and ρ were used to determine the probability. Interindividual variability (IIV) was modeled using additive error terms (η) as shown in equations 7 and 8.

$$\log(\lambda) = \log(TDUR) + \theta_\lambda + \eta_\lambda \qquad (7)$$

$$\log it(\rho) = \log\left(\frac{\rho}{1-\rho}\right) = \theta_\rho + \eta_\rho \qquad (8)$$

As mentioned earlier, the primary aim of this seizure count data analysis was to develop a suitable count model and subsequently, to develop a sequential PK-PD model using the PK model developed for the LTG concentration data in pregnant women (Chapter 2). Therefore, the possibility of an exposure-response model was explored using individual predicted concentrations from the LTG PK model (Chapter 2). In addition, a time course change of seizures was explored by considering GA as a time covariate. Furthermore, presence of subpopulations (responders and non-responders) among pregnant women was investigated via the mixture model option in NONMEM (31).

The Akaike's information criterion (AIC) was used for model discrimination throughout the analysis. Model development was also guided by various goodness-of-fit criteria, including diagnostic scatter plots and variance versus mean seizure count profiles (22), plausibility of parameter estimates, and precision of parameter estimates.

3.3 RESULTS

3.3.1 Subjects and seizure counts

The distribution of the seizure counts during the course of pregnancy and subject characteristics are presented in Table 3.1. The original dataset contained seizure count data for 73 subjects. Of these, only 39 subjects (30 whites, 7 blacks and 2 Asians) were epilepsy patients with both PK and seizure count data. Only these 39 subjects were considered for the analysis. Thirteen subjects had no seizures throughout the observational period. A total of 339 count observations were present in the analysis dataset. Of these, 69% were zero counts. A bar plot for distribution of seizure counts is presented in Figure 3.1. During the exploratory data analysis, the overdispersion phenomenon (variance > mean) was observed (Figure 3.2). The types of seizures were not considered in the analysis due to the small number of subjects representing each type of seizure in the dataset.

3.3.2 Seizure count data analysis

Although there was clear evidence of overdispersion in the data, the modeling of seizure counts was started by fitting the PS model (AIC = 1297.75). The PS model was compared with ZIP (AIC = 1032.23) and HDL (1047.39) models, which characterize the zero inflation of the seizure count data. Despite a decrease in AIC values with the zero inflation models, a plot of the average of the predicted conditional probabilities superimposed on the observed frequency of seizure counts exhibited deficiencies in characterization of the full nature of the observed data (Figure 3.3A). However, the zero inflation models performed better than the PS model in predicting lower seizure counts. Overall, above three models were not adequate to predict counts greater than or equal to 4.

The NB (AIC=829.06) and the ZINB (AIC=831.06) models were implemented to describe the observed overdispersion in the data (Figure 3.2). Both the models resulted with a high drop in AIC values (ΔAICs ~ - 468) compared to the PS model, and appeared to be similar in predicting the conditional probabilities (Figure 3.3B). In comparison to

the PS and the zero inflation models, both NB and ZINB models were found to be better in terms of predicting the counts between 0 and 6. However, similar to the PS and the zero inflation models, both NB and ZINB models failed to adequately predict counts greater than 6. With the above results, the NB model was selected to further explore the data due to its superiority to the PS and zero inflation models in terms of AIC and predictability as well as its similarity and reduced parameterization compared to the ZINB model.

Figure 3.4A and 3.4B depict the exposure-response relationship and the time course of the logarithm of seizure rate (seizure count divided by the time interval during which the seizures were recorded) with respect to GA, respectively. The LTG concentrations in the figure 3.4A are the concentrations predicted from the PK model presented in Chapter 2. Due to a high number of zero counts in the data, the smooth (as shown by in the Figure 3.4A and 3.4B), which indicates a possible relationship, was pulled toward 0. The presence of subpopulations (i.e., responders and non-responders) in the data was investigated via a mixture model option (29) within the selected NB model. The idea was to differentiate patients who demonstrate an exposure-response relationship with LTG treatment and time course changes of seizures with respect to GA, and those who do not. However, the mixture model indicated that there were 7% non-responders (~ 3 subjects) in the population with a non-significant estimate for the mixture probability (i.e., 95% confidence intervals included the null value zero). Therefore, the idea of sequential PK-PD and time course modeling of seizures was determined to be not feasible.

The first order MAK feature was implemented in the selected NB model (NBMAK model) to explore the influence of previous visit seizures on the current visit seizures. The NBMAK model resulted with non-significant overdispersion parameter estimates for the scenarios PDV=0 and PDV=1. Moreover, the precision of fixed effect and random effect parameters was very poor (73 – 373%) with the NBMAK model.

Based on model predictions, AIC value, plausibility of parameter estimates and better parameter precision values, the NB model was selected as the best possible model to describe seizures in pregnant women, who were on LTG therapy. The final model

parameter estimates including precision information are presented in Table 3.2. The calculated estimate of the population mean weekly seizure count (exp[θ_λ]) was expectedly low (0.04 seizures per week) as the data contained 69% zero seizure counts. The estimated ψ was high (1.74), indicating a high degree of overdispersion in the dataset (ψ = 0 indicates equidispersion). The IIV of the population mean weekly seizure counts was considerably high (227% CV). The model was unable to support inclusion of an IIV term on ψ. No substantial η-shrinkage was computed for θ_λ (16%).

A diagnostic plot representing individual predicted seizure counts versus observed seizure counts is shown in Figure 3.5A for the final NB model. The plot exhibits a uniform spread across the line of identity. However, the model underpredicted the counts at higher values. The observed overdispersion (Figure 3.2) in the data was reasonably handled by the NB model (Figure 3.5B). However, the NB model appeared to predict the seizures with high variance for the individuals with higher mean counts. Overall, the final NB model is appeared to be the best possible model to describe the seizures in the present dataset.

3.4 DISCUSSION

The aim of this analysis was to describe seizure frequency in pregnant women taking LTG monotherapy or LTG without any interacting drugs and subsequently, to establish an exposure-response relationship, and to characterize time course changes of seizures. Simple models with and without accounting for the zero inflation (PS, ZIP and HDL models) failed to adequately describe the seizure frequency in pregnant women. The NB and ZINB models were similar and were better than the more simple models (PS, ZIP and HDL models) in describing the seizures in pregnant women with epilepsy. Establishment of an exposure-response relationship (Figure 3.4A) and a time course (Figure 3.4B) describing the characteristics of seizures with respect to GA failed due to a high percentage of zero counts (69%) in the dataset. The use of a mixture model was found to be futile in dividing the women into responders and non-responders because a non-significant mixture probability was estimated in the analysis. Previous visit seizures failed to influence the current visit seizures in the pregnant women. The NB model

appeared to be the best possible model to describe the seizure count data based on plausibility of parameter estimates, better parameter precision values, better predictability of conditional probabilities compared to other models (Figure 3.3B *vs.* Figure 3.3A) and AIC value. The mean weekly seizure count was low with a value of 0.04 reflecting a large number of women who were well-controlled on their medication resulting in zero seizures in the study time intervals. The NB model reasonably characterized the overdispersion observed in the seizure count data.

To our knowledge, this is the first report that applied nonlinear mixed-effects modeling approach to explore seizure counts in pregnant women, who were on LTG therapy. Our study reports a low rate of seizures (0.04 seizures/week) in pregnant women regardless of the stage of pregnancy. Clinically, this is an encouraging result as there were fewer seizures in pregnant women even though LTG oral clearance is reported to increase up to 250% during pregnancy (10,13,14,16,17). The result indicates low risk for the mother and the developing fetus. As LTG levels were routinely monitored and doses were adjusted during the study, we attribute the result of low seizure rate to effective therapeutic drug monitoring. Clinical count data often exhibit an overdispersion phenomenon (variance > mean). In our analysis, the overdispersion observed (Figure 3.2) in the data was reasonably handled by the NB model (Figure 3.5B).

Our study has limitations with regards to design and the data collection. The study was an observational prospective study to investigate the time course changes of pharmacokinetics of AEDs during pregnancy but not designed to evaluate seizure frequency changes in pregnant women. Therefore, we were unable to characterize the time course changes of seizures with respect to GA. Our study was not statistically powered for the intended analysis. The seizures were not recorded in uniform intervals of time. Seizures recorded over the same length of time intervals would ensure uniform resolution of the data collected and an easier implementation of count models.

In conclusion, our limited data suggest that the mean weekly seizure counts are low in pregnant women due to effective therapeutic drug monitoring. We were unable to explore the predictors for seizures in the analysis. In order to better understand the seizure

frequencies in pregnant women, additional studies with larger sample size are needed to be designed (statistically powered) specifically to account for the seizure frequencies. In addition, studies with seizures recorded in uniform interval of times (i.e., uniform resolution) over the course of pregnancy are more advantageous.

Table 3.1. Summary of patient baseline characteristics and seizure counts

Baseline characteristics	**Mean ± SD or number**
No. of subjects	39
Age (in years)	30.0 ± 5.7
Body weight (in lbs)	133 ± 38.3
Height (in inches)	64.8 ± 2.6
BMI (in kg/m^2)	18.9 ± 10.5
Race	
Whites	30
Blacks	7
Asians	2
Seizure counts	
Preconception	15
Trimester 1	36
Trimester 2	59
Trimester 3	112
Postpartum	117

Table 3.2. Final model parameter estimates

Population Parameter	**Estimate (%RSE)**	**95% CI**
θ_λ	-3.24 (14.3%)	-4.15, -2.33
ψ	1.74 (14.9%)	1.23, 2.25
ω^2_λ (% CV)	5.16 (227%)	1.77, 8.55

% CV: percent coefficient of variation; %RSE: percent relative standard error; CI: confidence interval

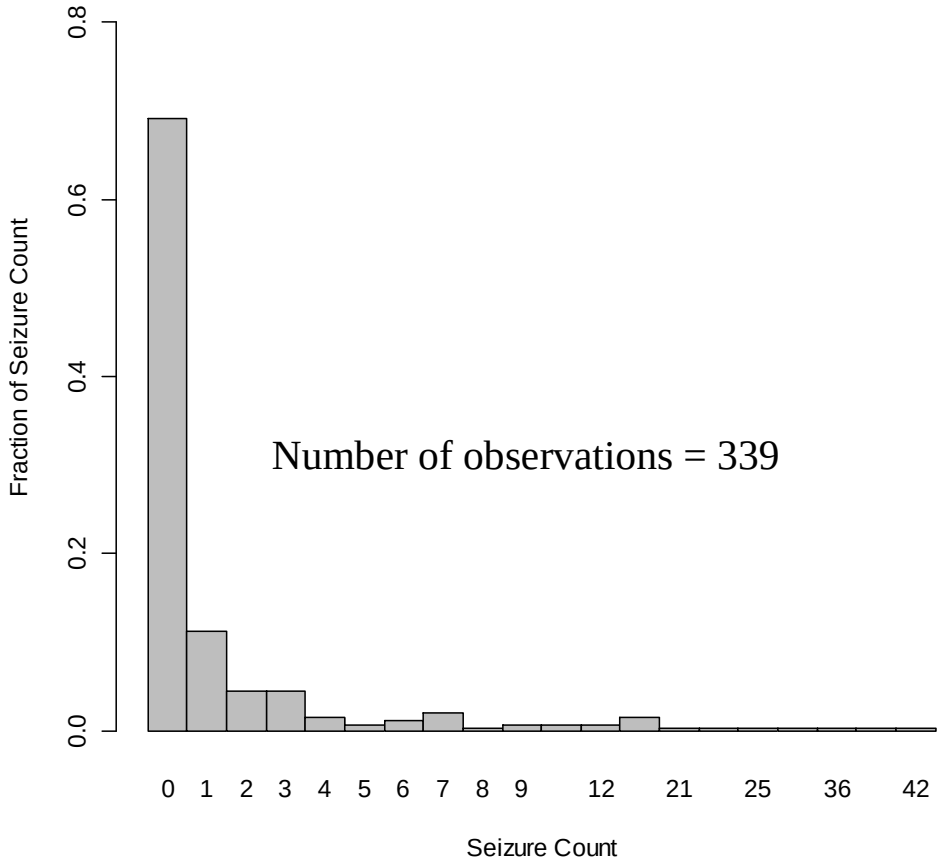

Figure 3.1. Distribution of seizure counts. Each bar represents a fraction of a particular seizure count in the raw data.

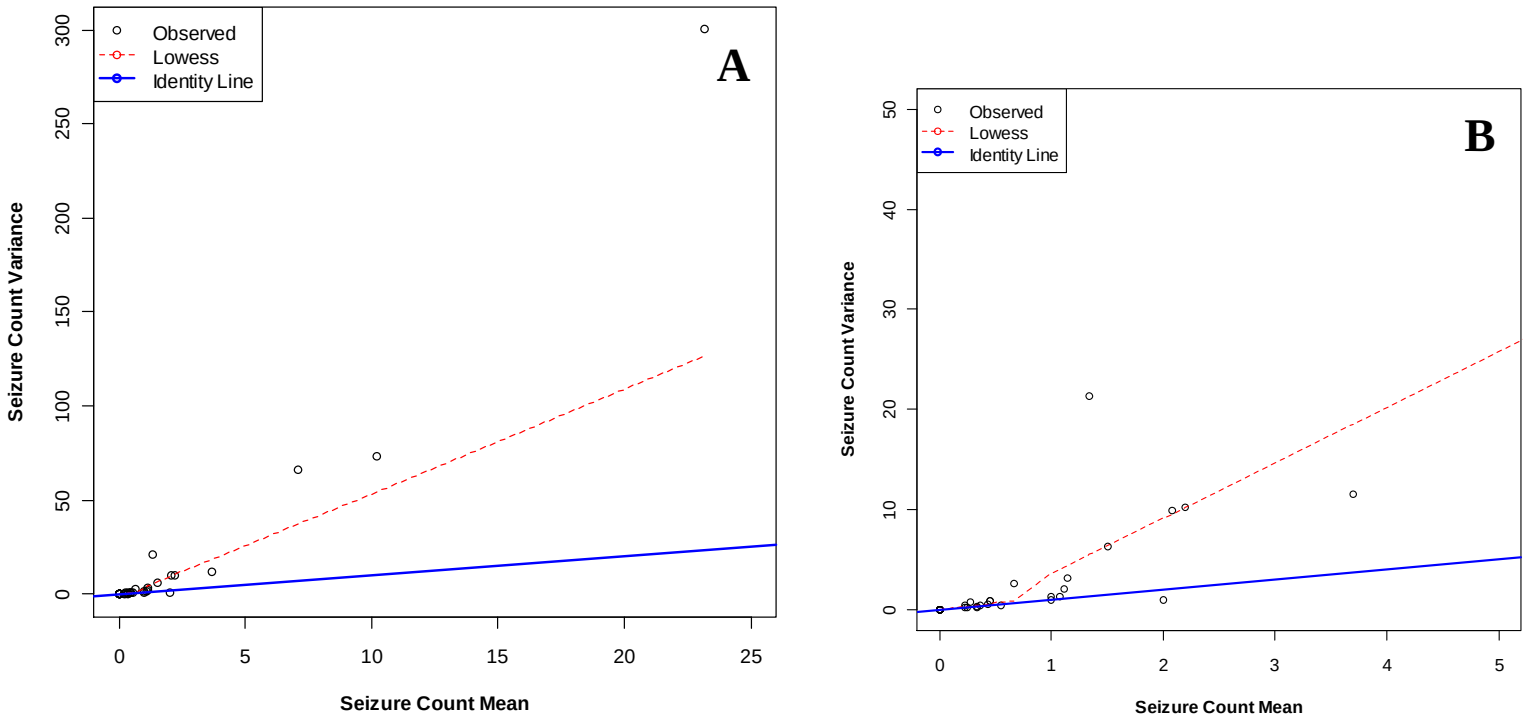

Figure 3.2. Variance *vs.* mean of seizure counts obtained from the raw data. Each data point represents one patient. Blue line represents the line of identity. Red dashed line represents the lowess (smooth) through the data. Plot A represents all the individuals and plot B represents the patients with mean of seizure counts less than 5.

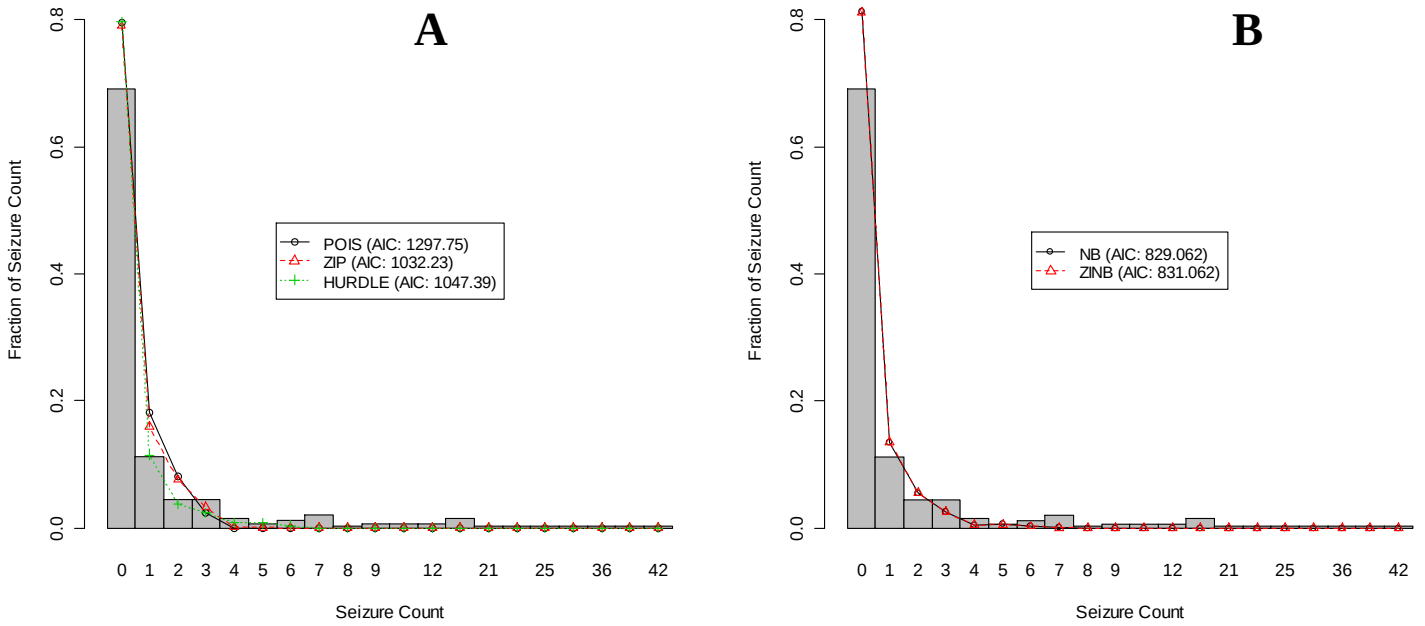

Figure 3.3. Model comparison plots for the PS, ZIP and HDL models (**A**), and for the NB and ZINB models (**B**). Each bar represents a fraction of a particular seizure count in the raw data. Points represent the average of predicted conditional probabilities from the respective models (as shown in legend of the plot). The lines connect the average conditional probabilities.

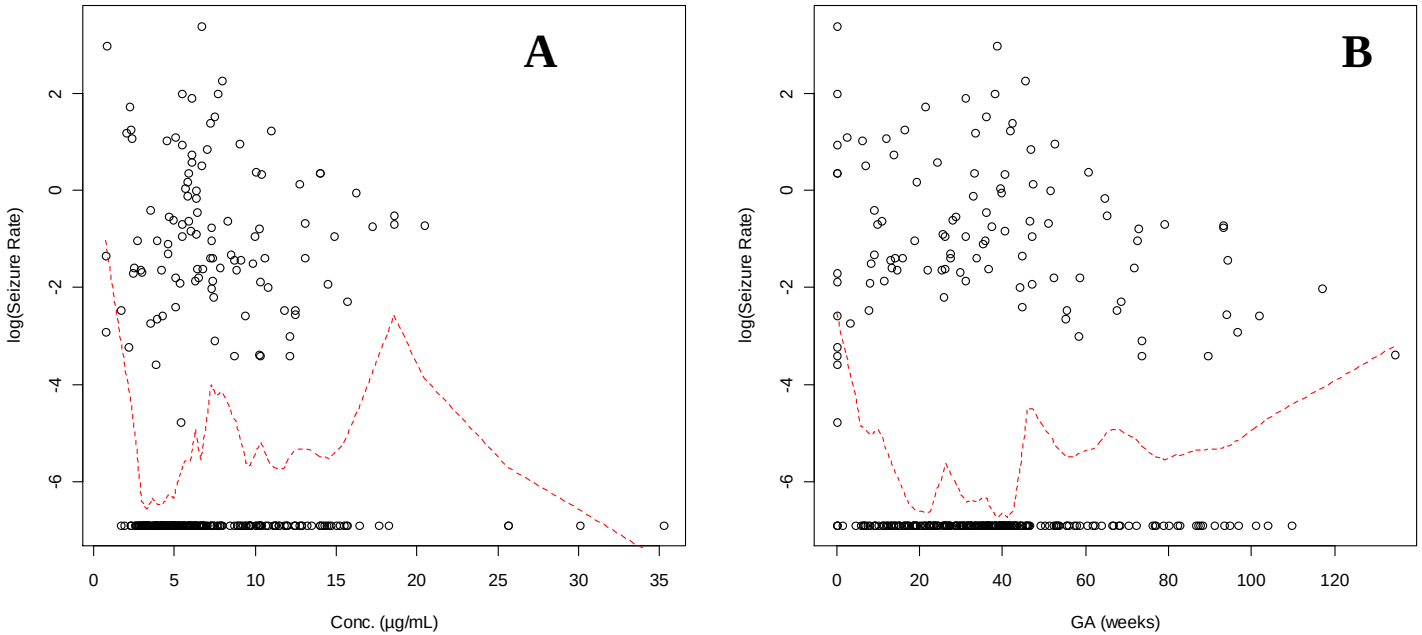

Figure 3.4. Plot A depicts the exposure-response relationship between predicted concentrations from LTG pharmacokinetic model and logarithm of seizure rates. Plot B depicts the time course changes of seizures with respect to gestational age (GA). Red dotted line represents the lowess (smooth) through the data.

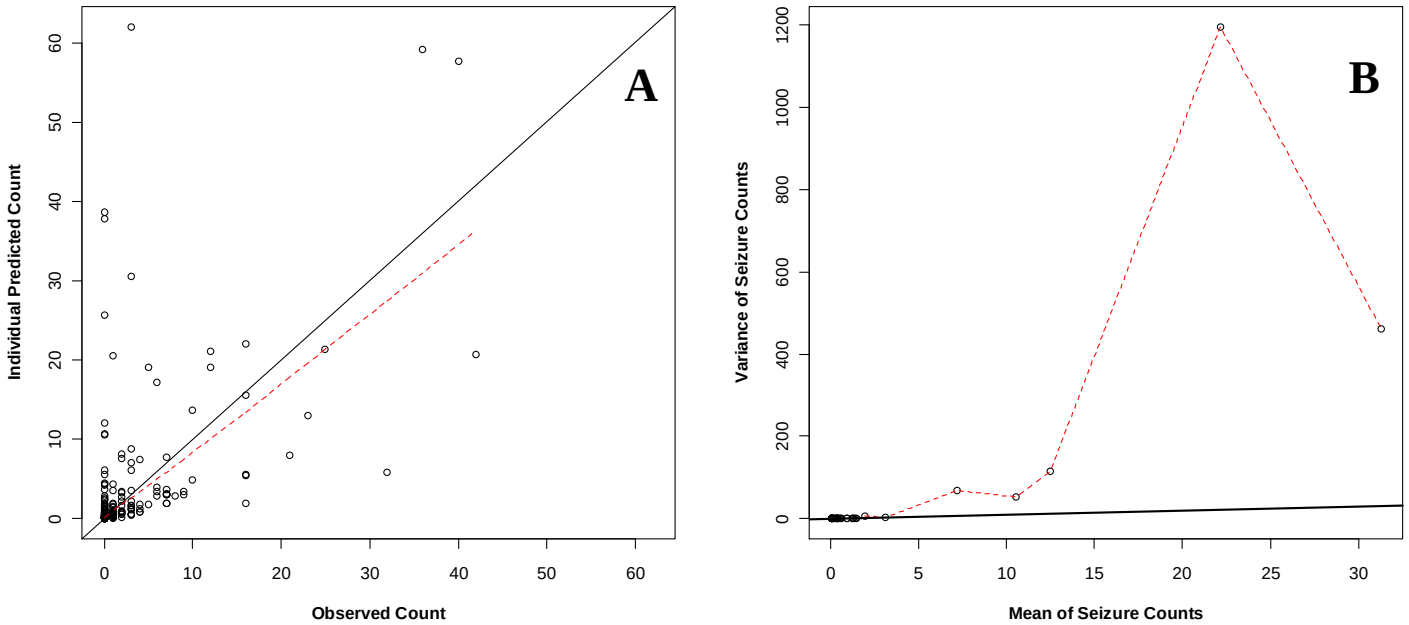

Figure 3.5. Final model (NB model) diagnostic plots. Plot A represents the individual predicted seizure counts *vs.* observed seizure counts. Plot B represents the variance *vs.* mean of individual predicted seizure counts from the final model. Black line represents the line of identity and red dashed line represents the lowess (smooth) through the data.

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CHAPTER 4

LAMOTRIGINE PHARMACOKINETICS FOLLOWING ORAL AND STABLE-LABELED INTRAVENOUS ADMINISTRATION IN YOUNG AND ELDERLY EPILEPSY PATIENTS

4.1 INTRODUCTION

Lamotrigine (LTG), a new generation antiepileptic drug (AED), is approved by the US FDA for the treatment of several types of seizures. LTG pharmacokinetics (PK) have been well characterized in adult healthy volunteers and adult patients with epilepsy (1–11). The immediate release LTG oral formulation is rapidly absorbed with negligible first-pass metabolism and 98% bioavailability in healthy volunteers (12). LTG is a low clearance drug and is extensively (~90%) metabolized via glucuronidation by UGT1A4 (9,13). It is a moderately protein bound (55%) (9) and has a relatively long half-life (23-37 h) (4–11).

However, there is limited PK information in elderly patients, and LTG may be better tolerated than other AEDs in the elderly due to a lower incidence of somnolence and rash (14,15). In addition, LTG has a low propensity to cause drug interactions since it is primarily glucuronidated and does not induce P450 expression. Age-related physiological changes in the elderly may affect drug disposition characteristics such as absorption, distribution, metabolism and elimination (16,17). Therefore, the LTG PK may differ between younger adults (18-60 years) and elderly (>60 years). A limited number of studies investigated the effect of age on LTG PK (18–22) and to date only two studies compared the PK characteristics between younger and older populations (5,23) but the effect of age on LTG PK is still not clear in the literature.

Accurate PK characteristics are important in devising optimal dosing strategies for patients taking continuous LTG therapy. Detailed information on LTG PK has limited to oral dosing due to the non-availability of an intravenous (*i.v.*) formulation. A stable isotope methodology allows simultaneous administration of *i.v.* and oral LTG under steady-state conditions without disrupting maintenance therapy in patients. Therefore, the methodology permits rigorous characterization of LTG PK in a clinically relevant setting. The methodology allows determination of absolute bioavailability, clearance, volume of distribution, and elimination half-life in patients on regular maintenance therapy.

The objectives of the study were to investigate the effect of age on the PK parameters of LTG, to estimate parameter variability in the study population, and to ascertain the

relationship between patient-specific covariates and PK parameters, in particular clearance of LTG.

4.2 METHODS

The study protocol was approved by the institutional review boards of three epilepsy research centers: the University of Minnesota, the University of Miami and Emory University. Use of stable labeled LTG ($^{13}C_2$, ^{15}N-LTG: SL-LTG) was approved by the US FDA (IND #72,642).

4.2.1 Subjects

Patients were recruited from the three epilepsy research centers. The subjects were young (n=16, 18-48 years of age) and elderly (n=12, 63-87 years of age) epilepsy patients on a stable chronic therapy of LTG. Inclusion criteria for patients were either LTG monotherapy or with other non-interacting AEDs; and a stable maintenance regimen of LTG for at least 2 weeks. Exclusion criteria were patients with significant cardiac disease; those with severe kidney dysfunction (creatinine clearance <30 mL/min); or those with moderate-to-severe liver dysfunction (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] 3x upper limit of normal). Patients were informed of the study and written consents were obtained before enrollment. The study was performed at the general clinical research centers (GCRCs) of the participating epilepsy research centers.

4.2.2 Study design

An open-label study design was implemented. The subjects were instructed to fast overnight before the day of the study and not to take their morning oral LTG doses. Upon admission to the GCRC, a neurological examination was performed, and medical and medication histories were recorded. One blood sample was obtained prior to drug administration for predose concentration measurement, and for basic clinical laboratory screening, including measures of kidney (blood urea nitrogen [BUN] and serum creatinine [SCr]) and liver function (alanine aminotransferase [ALT], aspartate amintransferase [AST] and bilirubin). A 50 mg of *i.v.* SL-LTG (10 mg/mL in 30% w/v 2-

hydroxypropyl-β-cyclodextrin) was diluted with normal saline to a final volume of 15 mL and infused at a rate of 1 mL/min. Following the infusion, patients were given their usual morning LTG oral dose (LAMICTAL® tablets) minus 50 mg. Blood samples for the intensive PK determination of LTG and SL-LTG were collected at 5 min, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 24, 48, 72 and 96 h postdose from elderly patients, and at 5 min, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 10, 12, 24, 48, 72 and 96 h postdose from younger patients. The samples were centrifuged and plasma was stored at -80 ^{o}C until analysis.

4.2.3 Simultaneous assay of LTG and SL-LTG

Plasma samples were analyzed on a validated gas chromatography-mass spectrometry (GC-MS) simultaneous assay for the determination of LTG and SL-LTG concentrations. A 50 µL of internal standard (3,5- diamino-6-(2-methoxy-pheny1)- 1,2,4-triazine, lot no. BW A725C, Glaxo Wellcome Inc., Research Triangle Park, NC, USA) was mixed with 500 µL of patient plasma sample. The mixture was processed by two liquid-liquid extractions with a total of 4 mL methyl-*tert*-butyl ether. The supernatant was collected and dried under nitrogen. The dried extract was then reconstituted with 10% N- methyl-N- (*tert*- butyldimethylsilyl)- trifluoroacetamide + 1% *tert*- butyl- dimethylchlorosilane (MtBSTFA + 1% t- BDMCS, lot no. 5698 from Regis Technologies, Inc., Morton Grove, IL, USA) in toluene. All reconstituted samples were heated to 60 ^{o}C overnight to force the reaction to form a diamino-NH-TBDMS derivative. Following derivatization, the samples were injected onto a SGE Sol-Gel column (30 m x 0.25 mm; Austin, TX, USA). The separated compounds were measured with an Agilent 5973N MS detector operating at a temperature of 310 ^{o}C in selected ion mode at the following mass to charges ratio (m/z): internal standard (*m/z* = 388); LTG (*m/z* = 426 [M-71]); and SL-LTG (*m/z* = 431 [M-71]). All samples from an individual patient were analyzed in a single batch and compared against a triplicate standard curve ranging from 0.25 to 20 µg/mL in LTG concentrations, and 0.025 to 2 µg/mL in SL-LTG concentrations. Triplicates of low, medium and high quality control samples were employed in the analysis of each run. Quality controls for LTG were 0.75 (low), 7.5 (medium) and 16 µg/mL (high) and for SL-LTG were 0.075 (low), 0.75 (medium) and 1.6 µg/mL (high). Values of quality

samples were considered acceptable if the accuracy (%bias) was within ± 15% and precision (% CV) was <15% (24).

4.2.4 Population PK modeling

The concentration-time data were analyzed by nonlinear mixed-effects modeling (NONMEM version 7, ICON Development Solutions, Ellicott City, MD, USA) with a GNU Fortran 95 compiler on a Dell Precision 470 workstation (Dell, Round Rock, TX, USA) with Windows XP x64 Professional edition (Microsoft, Redwood, WA, USA). Diagnostic plots were constructed with the R statistics software (version 2.11.1) (25). An open one-compartment (subroutines ADVAN2, TRANS2) and a two-compartment model (subroutines ADVAN4, TRANS4) (26) were investigated to select a PK structural model that best described the LTG concentration-time data. The first-order conditional estimation method with η-ε interaction (FOCE-INT) was employed for all model runs. Both *i.v.* and oral data were simultaneously analyzed. The structural models were provided parameters in terms of clearance (CL), central volume of distribution (V_c), intercompartmental clearance (Q), peripheral volume of distribution (V_p), absorption rate constant (k_a), and absolute bioavailability (F).

Interindividual variability (IIV) in the PK parameters was modeled with an exponential error model (Equation 1). θ_i is the parameter estimate for the i^{th} individual and $TV\theta$ is the typical value of the parameter in the population. $\eta^{\theta i}$ are individual-specific random effects for the i^{th} individual and are assumed to be normally distributed with mean 0 and variance ω^2. The form of equation 1 imparts a log-normal distribution on the parameter of interest. The estimate of IIV was converted to an approximate percent of coefficient of variation (% CV).

$$\theta_i = TV\theta \times \exp(\eta^{\theta i}) \qquad (1)$$

Residual unexplained variability (RUV) is a quantity that explains the variability around each observed concentration (Equation 2). C_{ij} is the j^{th} observed concentration of the i^{th} individual and $\hat{C}_{ij}$ is the model-predicted concentration based on the individual parameters for i^{th} individual. ε_{ij} is the residual error component of RUV, for j^{th}

observation in i^{th} individual and is assumed to be normally distributed with mean 0 and variance σ^2.

$$C_{ij} = f(\hat{C}_{ij}, \varepsilon_{ij}) \qquad (2)$$

RUV was explored with additive, proportional, and combined proportional and additive error models. Because *i.v.* and oral concentrations were measured with different dynamic ranges on a GC-MS and were modeled simultaneously, separate RUV models were examined for *i.v.* and oral data. A RUV model was selected based on Akaike Information Criterion (AIC) values and diagnostic plots.

η-shrinkage (Equation 3) was calculated to assess whether the individual data was informative for the empiral Bayes estimates. In addition, ε-shrinkage (Equation 4) was calculated to identify whether a perfect-fit phenomenon was taking place (27,28). $SD(\eta^{\theta i})$ denotes the standard deviation of individual's empirical Bayes estimates of the interindividual random effect. As defined above, C_{ij} and $\hat{C}_{ij}$ represent observed and model predicted concentrations, respectively. ω and σ are square rooted values of estimated variances of IIV and RUV, respectively.

$$\eta\text{-shrinkage} = 1 - SD(\eta^{\theta i})/\omega \qquad (3)$$

$$\varepsilon\text{-shrinkage} = 1 - SD((C_{ij} - \hat{C}_{ij})/\sigma) \qquad (4)$$

4.2.5 Covariate modeling

Once the base model (without patient-specific covariates) was developed, covariate model building was initiated. The covariates tested were age, body weight, sex, ethnicity, SCr, BUN, BUN/SCr ratio, albumin, ALT, AST, and creatinine clearance (CL_{CR}), which was calculated by Cockcroft-Gault equation (29). Age was included as both a continuous and a categorical covariate (young *vs.* elderly).

Initially, covariate modeling was guided by plots of empirical Bayesian estimates of PK parameters versus covariates or plots of η versus covariates. Covariate-parameter relationships were tested based on scientific principles or prior knowledge. Continuous covariates were normalized according to the median value observed in the dataset and

included in the model with a power function. Categorical covariates were tested with a multiplicative model in order to obtain the fractional difference of PK parameters between the tested categorical groups. Covariates were entered into the model in a multiplicative fashion. First, a univariate analysis was performed by adding one covariate at a time to the base model. A likelihood ratio test was employed for covariate selection by comparing objective function values (OFVs) obtained from NONMEM. A decrease in the OFV of at least 3.84 (χ^2, $p < 0.05$, $df = 1$) was considered significant in the univariate analysis. Second, a full model was developed with all significant covariates from the univariate analysis. Finally, backward elimination was performed to develop a final model. An increase in the OFV of at least 6.63 (χ^2, $p < 0.01$, $df = 1$) was considered significant in the backward elimination. The Akaike's information criterion (AIC) was used to compare non-nested models. Model development was also guided by various goodness-of-fit criteria, including diagnostic scatter plots, plausibility of parameter estimates, and precision of parameter estimates.

4.2.6 Model evaluation

A nonparametric bootstrap procedure (30) was used for model evaluation. One thousand data sets were generated by random sampling with replacement from the original data set using PDx-Pop 4.1 (ICON Development Solutions, Ellicott City, MD, USA). The final model was used to estimate population parameters for each bootstrap dataset. The bootstrap results were pooled only from the runs with successful convergence. The 2.5^{th}, 50^{th} and 97.5^{th} percentiles of the parameter distributions were computed and compared with the results from the population analysis.

In addition, the final model was qualified by examining standardized visual predictive check (SVPC) plots (31) separately for oral LTG and *i.v.* SL-LTG. The final model parameter estimates were used to simulate 1000 replicates of the original dataset. A percentile ($P_{i,j}$) for the j^{th} observation of the i^{th} individual was calculated (Equation 5) from the marginal distribution of the model-simulated concentrations as a function of time. $Ind_{ij,n}$, an indicator variable, equals 1 if j^{th} observed concentration of i^{th} individual is greater than the n^{th} model-simulated concentration of that individual at j^{th} time, and

equals 0 otherwise. The $P_{i,j}$ were then plotted against time after dose to construct the SVPC.

$$P_{i,j} = \frac{1}{1000}\sum_{n=1}^{1000} Ind_{ij,n} \qquad (5)$$

4.3 RESULTS

4.3.1 Study population

Intensive concentration-time data from simultaneous oral and *i.v.* administration of LTG and SL-LTG in 28 epilepsy patients (16 young and 12 elderly) were included in the population PK analysis. LTG daily doses ranged from 200 to 800 mg. Patient demographic information is shown in Table 4.1. The dataset included a total of 384 and 352 PK concentrations from oral LTG and *i.v.* SL-LTG, respectively. The patient population was predominantly female (68%). Of the 28 subjects, only one subject was an African American. Distribution of body weight was similar between young (n=16, 18-48 years) and elderly patients (n=12, 63-87 years). CL_{CR} in the young population was higher than in the elderly population (107 *vs.* 58 mL/min) indicating decreased renal function in the elderly patients. The majority of the elderly patients (CL_{CR}: 35-103 mL/min) had mild-to-moderate renal impairment as per FDA guidelines (32).

4.3.2 Population PK analysis

A two-compartment model with first order absorption and elimination (subroutine ADVAN4, TRANS4) adequately described the plasma concentration-time data. Semi-logarithmic scatter plots of observed concentrations versus time after dose for LTG (oral) and SL-LTG (*i.v.*) are presented in Figure 4.1A and 4.1B, respectively. Alpha and beta phases of the two compartmental PK model were well supported by the SL-LTG profile in Figure 4.1B. In the structural model evaluation, the OFV and AIC were significantly reduced (ΔOFV = -120, change in AIC [ΔAIC] = -112) with the two-compartment model compared to a one-compartment model. Each structural PK parameter including its IIV was successfully estimated. The RUV evaluation resulted in a single proportional error

model that adequately described both the LTG (oral) and SL-LTG (*i.v.*) concentrations. No additional benefit in terms of the ΔAIC was observed with additive, combined additive and proportional, or two separate RUV error models for LTG and SL-LTG concentrations.

4.3.3 Covariate modeling

During the univariate forward inclusion analysis, body weight, CL_{CR} and age (as a categorical covariate; young *vs.* elderly) had a significant effect on CL (ΔOFV > 3.84). Body weight and CL_{CR} significantly influenced V_c. The exponent estimate of body weight effect on V_c was 0.991. Since the estimate of the exponent was close to 1, it was fixed to an allometric exponent of 1 (33). Only body weight was found to be significant on intercompartmental clearance (Q) and none of the covariates affected V_p. No covariate showed a significant effect on k_a or *F*. Moreover, scatter plots of EBEs of PK parameters versus covariates or plots of η versus covariates did not suggest a possible effect of a covariate on k_a or *F* in the univariate analysis.

The full model was developed by incorporating all significant covariates into the base model. Body weight was allometrically scaled on Q and V_p in the full model by fixing the exponents to 0.75 and 1, respectively (33). When backward elimination was performed on the full model, CL_{CR} failed to reach a significant level on both total body CL and V_c. The resultant model was consistent with the elimination process of LTG, which is predominantly (>90%) metabolized by the glucuronidation pathway (9,13). Only body weight and age (as a categorical covariate) remained in the final model. The final forms of the equations for the model are given below:

$$CL = \theta_{CL} \times \left(\frac{WT_i}{70} \right)^{\theta_{WT,CL}} \times \theta_{Young,CL} \times e^{\eta_{CL}}$$

$$V_c = \theta_{V_c} \times \left(\frac{WT_i}{70} \right)^{1} \times e^{\eta_{V_c}}$$

$$Q = \theta_Q \times \left(\frac{WT_i}{70} \right)^{0.75} \times e^{\eta_Q}$$

$$V_p = \theta_{Vp} \times \left(\frac{WT_i}{70} \right)^{1} \times e^{\eta_{V_p}}$$

$$k_a = \theta_{k_a} \times e^{\eta_{k_a}}$$

$$F = \theta_F \times e^{\eta_F}$$

The final model parameter estimates including precision of the estimates are presented in Table 4.2. Based on the results, the population mean of LTG CL for a 70 kg (median body weight of patients in the study) elderly epilepsy patient was 1.31 L/h. On average, young patients have 37% higher CL than elderly patients. The population estimate for intercompartmental CL (Q) was 5.6 L/h for a 70 kg patient. The central (V_c) and peripheral (V_p) volumes of distribution for a 70 kg patient were estimated to be approximately 45 L and 17 L, respectively. The population mean for k_a was 0.56 h^{-1}. The *F* of the tablet formulation of LTG was estimated to be 75% with 95% bootstrap confidence interval ranged from 65% to 84%.

Typical value parameters for CL, V_c and *F* (<10% RSE) were estimated more precisely than Q, V_p and k_a (> 20% RSE). The IIV for Q, V_p and k_a was > 50%. Except body weight on Q and V_c, it was not possible to explain the variability of the parameters by other covariates. The IIV (%CV) was reduced considerably for CL (34%), V_c (34%) and Q (50%) in the final model compared to the base model IIV for CL (43%), V_c (42%) and Q (89%). The population estimate of RUV was moderate (21% CV), suggesting that there was minimal composite error of model misspecification, assay variability, intraindividual variability and error in recording the doses or time of blood samples.

The η-shrinkage was computed for the structural parameters from the final model: CL = 0.4%, V_c = 3.3%, Q = 51.1%, V_p = 17.4%, k_a = 26.6% and F = 3.3%. The substantial η-shrinkage (> 20-30%) for Q and k_a may be attributed to the lack of enough information about the parameter estimation from the individual concentration-time data (27,28). No substantial ε-shrinkage (7.6%) was computed, thereby indicating the adequacy of the model.

Goodness-of-fit plots for oral LTG and *i.v.* SL-LTG from the base model and the final model are presented in Figure 4.2 and 4.3. The diagnostic plots revealed that the final model was consistent with the observed data. Plots of conditional weighted residuals (CWRES) were generally well scattered across the range of predicted concentrations (Figure 4.2F and 4.3F) and time after dose (Figure 4.2H and 4.3H) with most of the data being within 3 units from the zero-ordinate indicating no overall systemic bias in the model diagnostics.

4.3.4 Model evaluation

The results of the bootstrap procedure (855 successful runs) are presented in Table 4.2. The estimated model parameters from population analysis and bootstrap analysis were highly comparable. Furthermore, 95% CI of the population parameters were comparable to the bootstrap 2.5^{th} and 97.5^{th} percentiles. Thus, the model evaluation indicates the accuracy and precision of parameter estimates as well as stability of the model.

The SVPC plots of oral LTG and *i.v.* SL-LTG are shown in Figure 4.4A and 4.4B, respectively. From the plots, it was observed that the $P_{i,j}$ values for the observed LTG and SL-LTG concentrations were in general uniformly well distributed between 0 and 1. Approximately 5% and 8% of $P_{i,j}$ values were outside 5^{th} and 95^{th} percentiles for LTG and SL-LTG, respectively. These results suggest that the data has been reasonably well described by the PK model with good predictive performance.

4.4 DISCUSSION

Stable isotope methodology allowed simultaneous administration of oral and *i.v.* formulations of LTG under steady-state conditions without disrupting maintenance therapy. This methodology allowed rigorous characterization of LTG PK in the patients. LTG CL differed between young and elderly patients with epilepsy and was influenced by a patient's body weight. Other PK parameters such as intercompartmental clearance (Q), central (V_c) and peripheral (V_p) volumes were influenced by body weight. None of the covariates influenced k_a and F.

The absolute bioavailability (F) for the LTG tablets dosed in young and elderly epilepsy patients was 75%. The only other study that reported F (98%) was done in a small study (n=8; healthy volunteers; 20-35 years) with an *i.v.* LTG isethionate salt preparation and oral LTG gelatin capsules. In our study, the use of SL-LTG allowed for evaluation of F in patients on maintenance therapy with simultaneous administration compared to the classic two-period crossover design.

The plasma concentration-time profiles of oral LTG and *i.v.* LTG were adequately described by a two-compartment PK model. Previous population PK studies (18–22,34,35) described LTG PK by a one-compartment model; however, the studies did not include *i.v.* PK data in the analyses.

The final population estimate for k_a was 0.56 h^{-1}, which is lower than the values (1.3-3.57 h^{-1}) reported in the literature (9,21,22). However, our k_a estimate was close to the value (0.38 h^{-1}) reported from a population PK study in Indian epilepsy patients (34). As we employed intensive sampling in the study and an adequate number of samples collected during the absorption phase, we expect that the k_a estimate is fairly reliable. The IIV in k_a was 140%, which falls in the range of previous values (77.5% - 156%) reported from population PK studies (21,35).

In our analysis, we found LTG CL to be influenced by age (young [18-48 years] *vs.* elderly [63-87 years]), and the elderly patients to have an average of 27% lower CL than younger adults of comparable body weight. Similarly, previous studies in healthy

volunteers and patients with epilepsy reported a 37% difference in CL (intensive single dose oral PK; elderly [n=12; 26-38 years] *vs.* young [n=12; 65-76 years]) and a 20% lower LTG oral clearance in the older than younger adults (retrospective outpatient study; old [n=155; 55-92 years] *vs.* young [n=247; 16-36 years]), respectively (5,23). Age-related changes in liver mass could explain the difference in CL between the elderly and younger patients (36–38). However, given the low extraction ratio and moderate protein binding (55%) characteristics of LTG, we expect the reduction in CL to be mainly caused by the reduced enzyme capacity (or UGT1A4 expression) and/or liver volume in the elderly group (37,38). It has often been assumed that age has no effect on glucuronidation (36,39). The hypothesis was based on PK studies of lorazepam and oxazepam by Greenblatt and coworkers conducted in the late 1970's prior to identification of multiple UGT isoforms (40,41). Lorazepam and S-oxazepam are UGT2B15 substrates and R-oxazepam is glucuronidated by UGT2B7 and UGT1A9 (42–44). In contrast, LTG is a UGT1A4 substrate, an enzyme that is independently regulated *vs.* UGT2B15 (on different chromosomes). Therefore, individual UGT probes may show age-selective differences in expression and should not be generalized to a single conjugation (Phase II metabolism).

The volumes (V_c and V_p) were only affected by body weight of the patients. An apparent steady-state volume of distribution (V_{ss}/F) was calculated as a sum of apparent central (V_c/F) and peripheral (V_p/F) volumes of distribution and was found to be 83 L. This value is in close agreement with the apparent volume of distribution (V/F) values (77.1 L - 132 L) reported in the literature (4–6,8,9,19–22). A mean terminal half-life ($t_{1/2\beta}$) of LTG was derived from the final model parameter estimates for both young and elderly epilepsy patients. The mean $t_{1/2\beta}$ was 24.6 h and 33.6 h for young and elderly epilepsy patients, respectively. This result is in close agreement with the result (6.3 hour longer) presented by Posner et al (5) that on average elderly have a nine hour longer terminal half-life compared to younger population.

The results of η- and ε-shrinkage confirm the reliability of empirical Bayes estimates, parameter-covariate relationships and adequacy of the final model (27,28). The bootstrap analysis results were similar to the final model estimates. This suggests that the

population PK parameters from the final model are reliable. The $P_{i,j}$ values in the SVPC plots were well distributed between and 0 and 1, and <10% $P_{i,j}$'s fell outside of the region between 5^{th} and 95^{th} percentiles. This indicates the data is well described by the final model with good predictive performance.

In conclusion, we characterized LTG PK with the simultaneous *i.v.* and oral PK data and compared the PK differences between young and elderly patients with epilepsy. After adjusting for body weight in our population, LTG CL in the elderly was 27% lower than in younger patients with epilepsy. These results may support a dose adjustment based on age where an elderly patient would receive, on average, 73% of the dose prescribed for a younger adult. No difference in *F* for the LTG tablets was found between the two age groups; however, the 75% absolute bioavailability in patients on maintenance therapy was lower than the reported 98% in healthy volunteers (8,12).

Table 4.1. Patient characteristics in all subjects, young and elderly patients

Patient Characteristics	**All subjects (n=28)**	**Young (n=16)**	**Elderly (n=12)**
Categorical variables	**Frequency, n (%)**		
Sex			
Male	9 (32%)	4 (25%)	5 (42%)
Female	19 (68%)	12 (75%)	7 (58%)
Race			
Whites	27 (96%)	15 (94%)	12 (100%)
African Americans	1 (4%)	1 (6%)	0 (0%)
Ethnicity			
Hispanic/Latino	19 (68%)	16 (100%)	3 (25%)
Non-Hispanic/non-Latino	9 (32%)	0 (0%)	9 (75%)
Continuous variables	**Median (range)**		
Age (yr)	43.5 (18-87)	32 (18-48)	70.5 (63-87)
Body weight (kg)	70.2 (48.3-119.7)	70.2 (48.3-117.3)	70.2 (49.1-119.7)
Serum creatinine (SCr) (mg/dL)	0.9 (0.7-1.8)	0.9 (0.7-1.1)	1.0 (0.8-1.8)
Creatinine clearance (mL/min)	80.4 (34.6-226)	107.1 (60.8-226)	58.1 (34.6-103.2)
Blood urea nitrogen (BUN) (mg/dL)	15 (9-46)	12.5 (9-23)	21.5 (13-46)
BUN/SCr ratio	16.6 (10-30.9)	14.1 (10-24.5)	21 (15-30.9)
Albumin (g/dL)	4.1 (3.6-8.7)	4.1 (3.6-8.7)	4.2 (3.9-4.5)
Aspartate aminotransferase (g/dL)	22 (11-74)	20 (14-45)	23.5 (11-74)
Alanine aminotransferase (g/dL)	22 (12-71)	24 (12-71)	21 (12-36)
Hematocrit (%)	38.3 (28.7-45.8)	38.7 (32.4-45.8)	37.8 (28.7-43.5)

Table 4.2. Final parameter estimates from population analysis and bootstrap analysis

Parameter	Population analysis		Bootstrap analysis	
	Estimate (%RSE)	**95% CI**	**Median**	**2.5^{th}, 97.5^{th} percentile**
CL (L/h)				
θ_{CL}	1.31 (9.7%)	1.06, 1.56	1.29	1.07, 1.61
$\theta_{WT, CL}$	0.93 (32.8%)	0.33, 1.52	0.91	0.08, 1.53
$\theta_{Young, CL}$	1.37 (13.4%)	1.01, 1.73	1.38	1.03, 1.77
V_c (L)				
θ_{Vc}	45.1 (7.8%)	38.2, 52.0	45.2	37.9, 52.6
$\theta_{WT, Vc}$	1 (fixed)	-	-	-
Q (L/h)				
θ_{Q}	5.63 (29.8%)	2.34, 8.92	5.31	1.91, 16.5
$\theta_{WT, Q}$	0.75 (fixed)	-	-	-
V_p (L)				
θ_{Vp}	17.2 (21.7%)	9.87, 24.5	17.8	10.23, 27.9
$\theta_{WT, Vp}$	1 (fixed)	-	-	-
k_a (h^{-1})				
θ_{ka}	0.56 (40.8%)	0.11, 1.00	0.55	0.10, 1.33
***F* (absolute bioavailability)**				
θ_{F}	0.75 (5.6%)	0.68, 0.83	0.75	0.65, 0.84
Interindividual variance (IIV)				
ω^2_{CL}	0.12 (34.1% CV)	0.06, 0.17	0.10	0.05, 0.16
ω^2_{Vc}	0.12 (34.2% CV)	0.05, 0.18	0.11	0.06, 0.19
ω^2_{Q}	0.25 (50.3% CV)	-0.07, 0.57	0.22	0.00002, 0.98
ω^2_{Vp}	0.71 (84.3% CV)	0.06, 1.36	0.68	0.19, 2.57
ω^2_{ka}	1.97 (140% CV)	-0.42, 4.36	1.5	0.00005, 6.37
ω^2_{F}	0.07 (26.9% CV)	0.03, 0.11	0.06	0.03, 0.11
Residual unexplained variability (RUV)				
σ^2_{prop}	0.04 (21.0% CV)	0.03, 0.06	0.04	0.03, 0.06

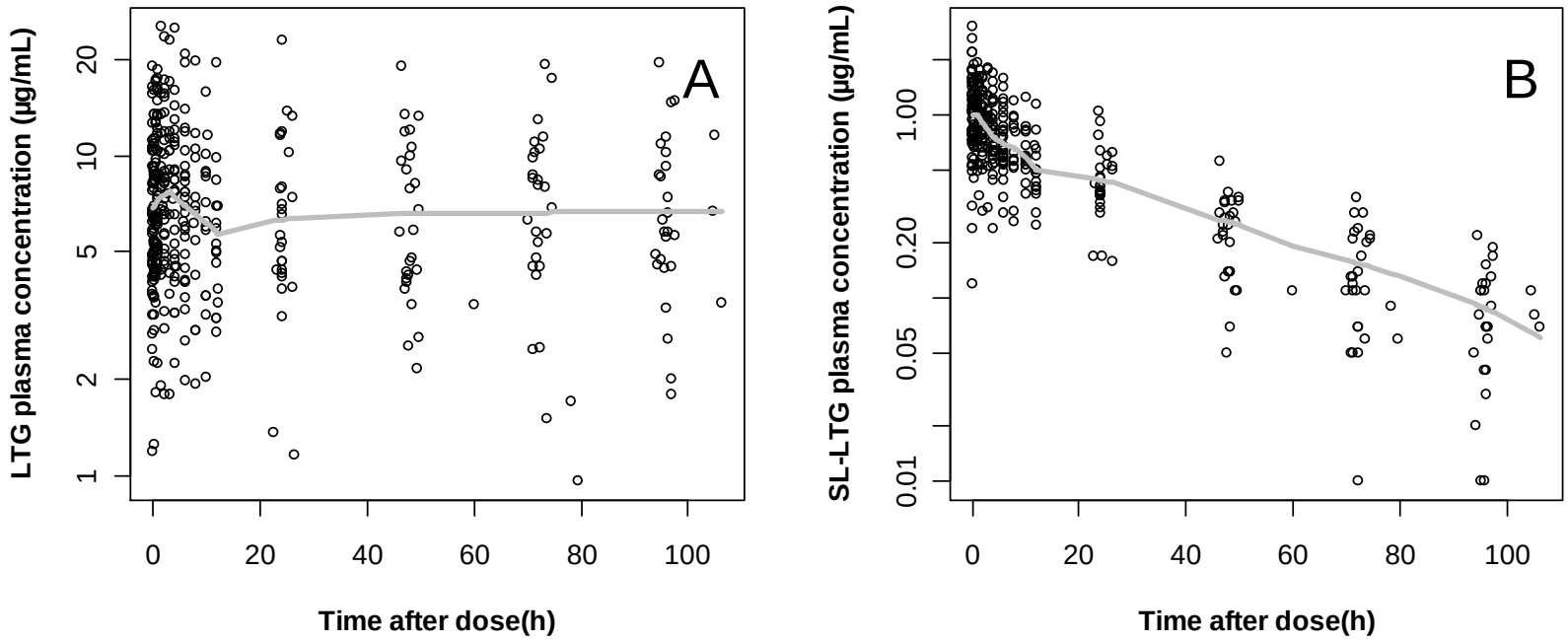

Figure 4.1. Semi logarithmic observed concentrations (µg/mL) *vs.* time after dose (h) scatter plots for oral LTG (A) and *i.v.* SL-LTG (B). Solid grey line is a smooth for concentrations *vs.* time after dose.

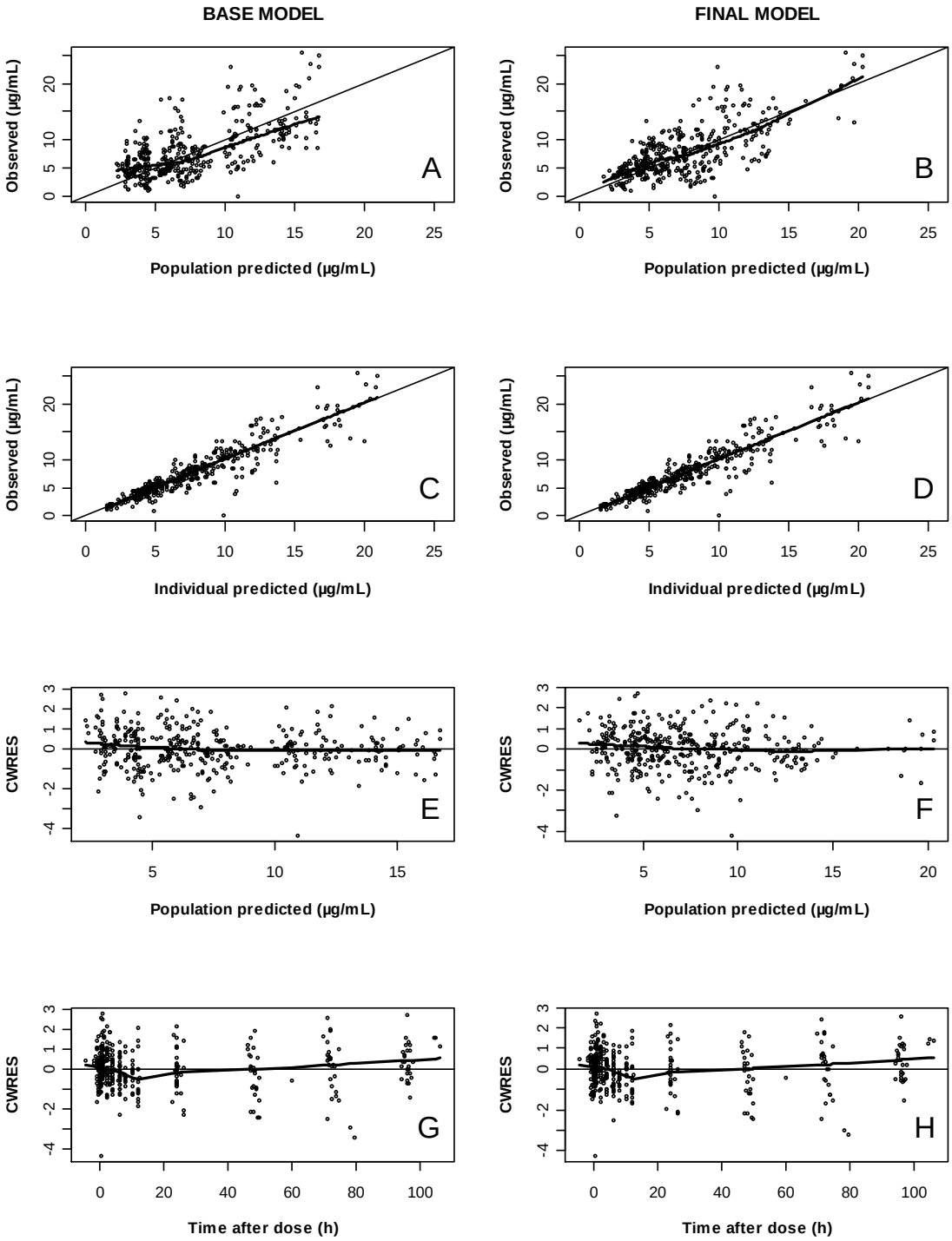

Figure 4.2. Goodness-of-fit plots for oral LTG from the base model (A, C, E and G) and the final model (B, D, F and H). CWRES, conditional weighted residuals.

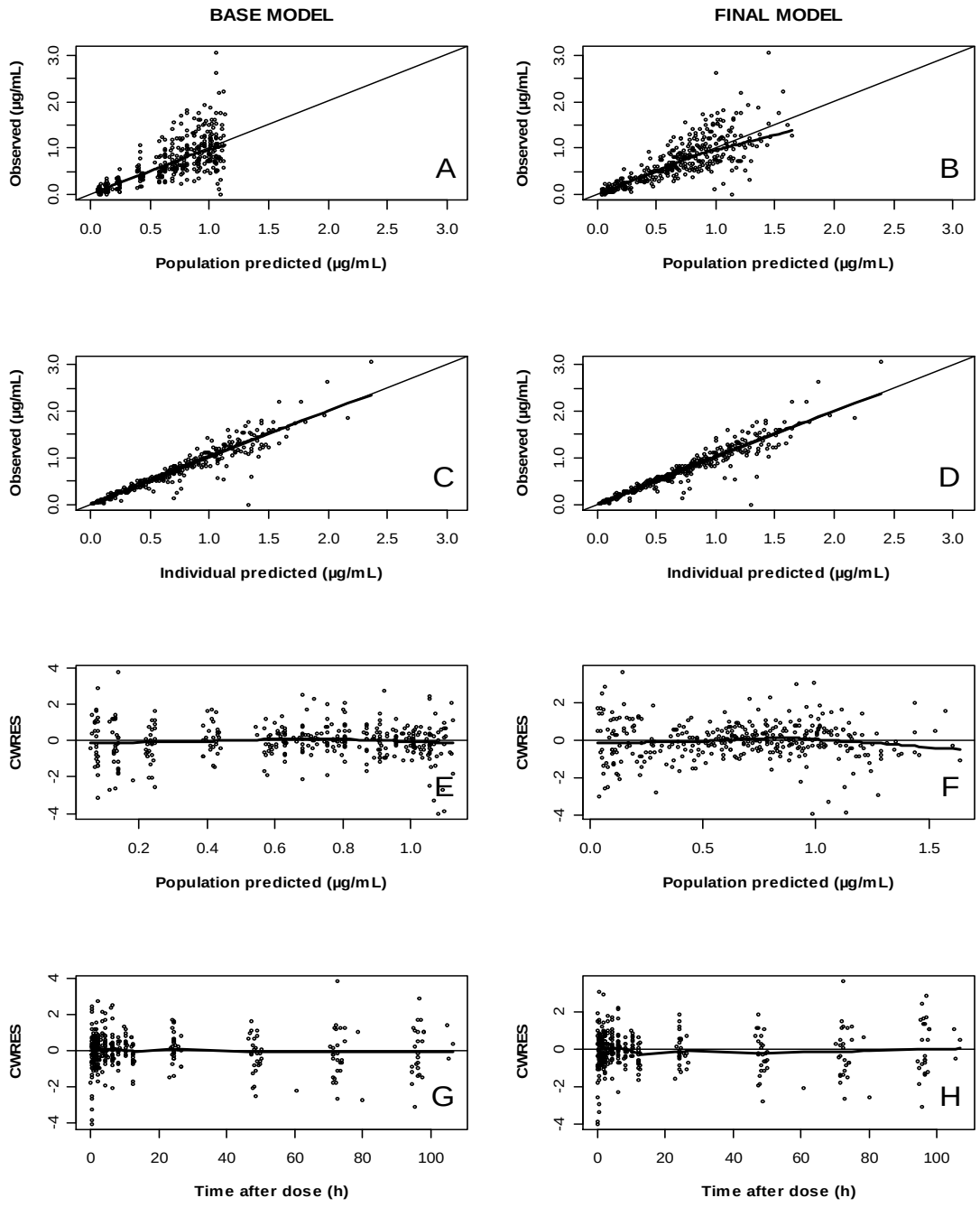

Figure 4.3. Goodness-of-fit plots for *i.v.* SL-LTG from the base model (A, C, E and G) and the final model (B, D, F and H): CWRES, conditional weighted residuals.

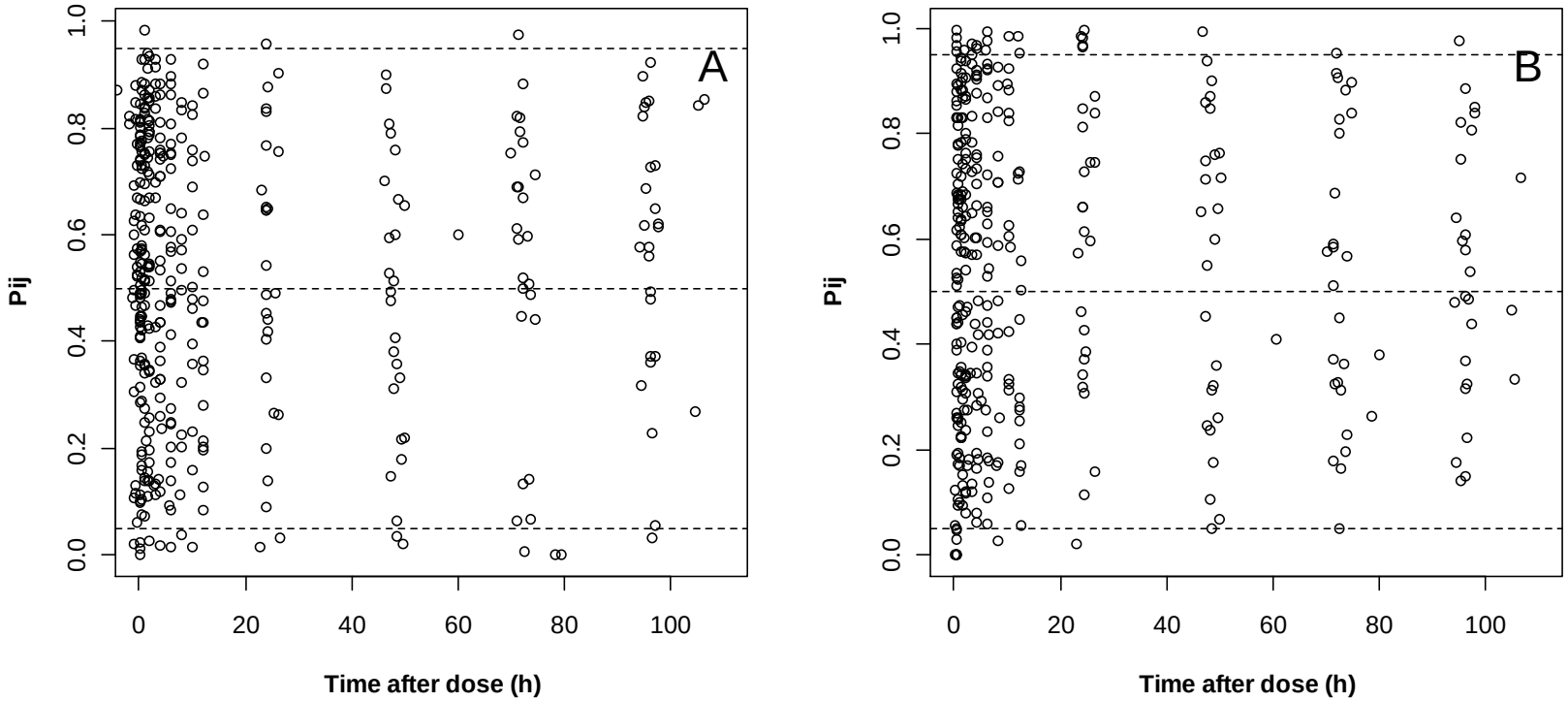

Figure 4.4. Standardized visual predictive check (SVPC) plots for oral LTG (A) and *i.v.* SL-LTG (B). P_{ij}, a percentile for the j^{th} observation of the i^{th} individual calculated from the marginal distribution of the model-simulated concentrations. Open circles, calculated $P_{i,j}$ values; dashed lines, 5^{th}, 50^{th}, and 95^{th} percentiles (from bottom to top).

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CHAPTER 5

STEADY-STATE PHARMACOKINETICS AND BIOAVAILABILITY OF IMMEDIATE RELEASE AND EXTENDED-RELEASE FORMULATIONS OF LAMOTRIGINE IN ELDERLY EPILEPSY PATIENTS: USE OF STABLE ISOTOPE METHODOLOGY

5.1 INTRODUCTION

Lamotrigine (LTG), 3,5-diamino-6(2,3-dichlorophenyl)-1,2,4-triazine, is structurally unrelated to existing antiepileptic drugs (AEDs) (1). LTG, the most commonly prescribed new generation AED (2,3), is approved for adjunctive therapy of partial seizures, primary generalized tonic-clonic seizures, generalized seizures for Lennox-Gastaut syndrome in adult and paediatric patients aged ≥ 2 years, for conversion to monotherapy in patients aged ≥ 16 years with partial seizures, and for maintenance therapy of bipolar I disorder in adults aged ≥ 18 years (4).

The pharmacokinetics (PK) of LTG have been well characterized in adult patients with epilepsy but there is limited information in elderly patients. LTG is better tolerated than the other AEDs in the elderly (5). The PK may alter with age (6,7). The elderly may exhibit a myriad of changes in gastrointestinal physiology with a great potential to influence drug absorption (8,9) Although a comparison oral PK study between young adults and elderly healthy volunteers characterized the PK in an elderly group (10), a PK study in elderly patients with epilepsy has not yet been reported. Moreover, an intravenous (*i.v.*) PK study that could characterize elimination or bioavailability in elderly patients has not been reported. Posner et al have demonstrated increased peak concentration (25%) and exposure (55%), an extended half-life (6.3 h longer), and reduced apparent oral clearance (35%) in elderly compared to young healthy adults (10). In contrast, two separate population pharmacokinetic studies showed no age effect on apparent oral clearance; however, few elderly subjects were included in the analyses (11,12). Moreover, a population pharmacokinetic study in elderly epilepsy patients reported oral clearance that is not different compared to oral clearance in adult population (13).

LTG immediate release (LTG-IR) formulation is rapidly and completely absorbed following oral administration with negligible first-pass metabolism and near complete bioavailability in healthy volunteers. It reaches peak plasma concentration in 1.3 – 4.7 h. The $t_{1/2}$ reduces to 24 h under steady-state conditions whereas it is 33 h after a single dose administration (4). LTG is a low clearance drug that is almost completely metabolized.

LTG undergoes biotransformation predominantly by N-glucuronidation, a conjugative pathway that is not significantly affected by age (6,14), with 75 – 90% recovered in urine as a major 2-N glucuronide metabolite and other minor metabolites including a 5-N glucoronide and N-2 methyl metabolite, unidentified metabolites and unchanged drug (15,16). *In vitro* metabolism studies suggest that human hepatic enzyme UGT1A4 is responsible for N-glucuronidation (17,18).

A new LTG extended-release (LTG-XR) formulation has been developed by Glaxo SmithKline and marketed as Lamictal® XR™. LTG-XR is currently approved for patients ≥ 13 years of age. LTG-XR enteric coated tablets are formulated by a modified release eroding matrix core (DiffCORE) that reduces the dissolution rate of LTG compared to LTG-IR and prolongs the drug release over approximately 12 – 15 h (19). The steady-state PK of LTG-XR compared to LTG-IR have been studied in subjects with epilepsy in an open-label crossover study (20). In a neutral metabolism group (no concomitant inducers or inhibitors), steady-state peak concentration values in serum are on average 11% lower (geometric mean: 6.83 *vs.* 7.82 µg.h/mL). Fluctuation index, (Cmax – trough concentration [Cτ])/Average concentration [Cavg], is reduced by 37% (geometric mean: 0.34 *vs.* 0.55). Tmax is extended from 1.5 h to 6 h after switching from LTG-IR to LTG-XR (20). In general, extended-release formulations reduce peak-to-trough fluctuation, and may have an improved adverse effect profile in comparison to immediate release formulations (21), but PK knowledge of an extended-release formulation is important to treat epilepsy.

Stable-labeled (nonradioactive) isotope forms of drugs are effective probes for PK and bioavailability studies (22). Stable isotope methodology permits the simultaneous administration of a drug by two routes or in two formulations. Subsequently, characterization of absolute and relative bioavailability in one single experiment can be done under steady-state conditions without disrupting the maintenance therapy. Furthermore, determination of clearance, volume of distribution and half-life can be done under steady-state conditions.

The objectives of this study were to evaluate relative and absolute oral bioavailability of LTG-IR and LTG-XR under steady-state conditions, and to characterize the LTG PK with stable isotope methodology in elderly patients with epilepsy.

5.2 METHODS

This was a classic two-period, crossover bioavailability study in elderly patients. The study was approved by the Institutional Review Board Human Subject's Committees at the University of Miami and the University of Minnesota. Consent to participate in the clinical research study was obtained from all subjects.

5.2.1 Study subjects

The subjects (n=12) were elderly patients >60 years of age on a stable chronic therapy of LTG-IR for a pre-existing medically defined need. The inclusion criteria for patients were a stable maintenance of LTG-IR regimen for at least 2 weeks; able to ingest oral medication; in good general health as confirmed by medical history and physical examination. The exclusion criteria were patients who had a significant unstable medical or psychiatric disorder; were known to have a history of drug or alcohol abuse or clinically significant alcohol use as determined by the investigators; had donated blood within 60 days prior to the study initiation; had chronic anemia; or were receiving drugs that could significantly effect the metabolism and clearance of LTG. Subjects were admitted to the General Clinical Research Center (GCRC) or the Infusion Center at the University of Miami. On arrival, blood pressure and pulse rate were recorded. Also, rhythm strip electrocardiogram (EKG) before, during, and 15 min after intravenous infusion of stable labeled LTG were recorded. Single blood sample was obtained for basic clinical laboratory screening, including measures of kidney (blood urea nitrogen [BUN] and serum creatinine [SCr]) and liver function (alanine aminotransferase [ALT], aspartate amintransferase [AST] and bilirubin).

5.2.2 Study formulations

The oral formulations, LTG-IR (LAMICTAL®) and LTG-XR (LAMICTAL® XR™), were obtained from Glaxo SmithKline, USA. The stable isotope form of LTG ($^{13}C_2$, ^{15}N-

LTG) was formulated for intravenous (*i.v.*) administration in a 30% w/v 2-hydroxypropyl-β-cyclodextrin (HPβCD) solution to make a final strength of 10 mg/mL. This formulation was prepared under good manufacturing practices by Pharmaceutics Division at the University of Iowa and was dispensed in 5 mL vials (IND 72,642). The formulation was diluted with normal saline to a final volume of 15 mL before being infused at the rate of 1 mL/min.

5.2.3 Study design

Subjects who were on chronic therapy of LTG-IR were first initiated with IR treatment phase and were switched to LTG-XR for a minimum of one week before being started with XR treatment phase. On both IR and XR study days, a 50 mg replacement tracer dose of LTG ($^{13}C_2$, ^{15}N-LTG) was given intravenously in a cyclodextrin based formulation with the oral LTG dose. Food was withheld for ~ 8 h before oral dosing and the subjects were instructed to take the food only 1.5 h postdose. Subjects maintained their total daily dose of LTG over both the phases of the study as follows:

- IR Treatment Phase – On the IR study day, subjects were intravenously infused with a 50 mg replacement tracer dose over 15 min, and were given their usual morning LTG dose (less 50 mg) immediately after the completion of infusion.

- XR Treatment Phase – Subjects were switched to LTG-XR for a minimum of one week. On the XR study day, subjects were intravenously infused with a 50 mg replacement tracer dose over 15 min, and were given their usual morning LTG dose (less 50 mg) immediately after the completion of infusion.

At the end of the study, subjects were instructed to continue maintenance therapy with commercially available LTG i.e. LTG-IR.

Blood samples for PK analysis were collected prior to simultaneous oral and intravenous LTG administration (predose) and at 5 min, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 24, 48, 72 and 96 h postdose. The samples were immediately centrifuged and plasma was transferred to separate containers for storage at -80 ^{o}C until analysis on GC-MS.

5.2.4 LTG analysis

LTG reference standard (3,5- diamino-6-(2,3-dichloro phenyl)-*as*-triazine), lot no. TRC-02080801, was obtained from Toronto Research Chemicals Inc., ON, Canada. Internal standard (33- diamino-6-(2-methoxy-pheny1)- 1,2,4-triazine), lot no. BW A725C was provided by Glaxo Wellcome Inc. (Research Triangle Park, NC, U.S.A.). Stable isotope of LTG ([$^{13}C_2$, ^{13}N]- 3,5- diamino-6-(2,3-dichloro phenyl)-*as*-triazine) shown in Figure 5.1, was obtained from Cambridge Isotope Laboratories, Inc., Andover, MA, U.S.A.

Plasma samples were thawed on bench top and then vortexed for 30 sec before extraction. A mixture of 50 µL of internal standard solution and 500 µL of each subject sample was processed by two liquid-liquid extractions with a total of 4 mL methyl-*tert*-butyl ether. The organic layer was dried on a Zymark nitrogen drying apparatus and reconstituted with 10% N- methyl-N- (*tert*- butyldimethylsilyl)- trifluoroacetamide + 1% *tert*- butyl- dimethylchlorosilane (MtBSTFA + 1% t- BDMCS, lot no. 5698 from Regis Technologies, Inc., Morton Grove, IL, U.S.A.) in toluene. All reconstituted samples were heated to 60 ^{o}C overnight to force the reaction to form a diamino-NH-TBDMS derivative. LTG and stable labeled LTG (LTG-SL) concentrations were simultaneously determined by a validated GC-MS method. The samples were injected onto an Agilent 6890 series GC system with an injector port temperature of 250 ^{o}C. A SGE Sol-Gel column (30 m x 0.25 mm) was used with an oven temperature at gradient of 100 ^{o}C to 300 ^{o}C to facilitate both speed and separation. The separated compounds were measured with an Agilent 5973N MS detector operating at a temperature of 310 ^{o}C in selected ion mode at the following mass to charges ratio (m/z): internal standard (*m/z* = 388); unlabeled LTG (*m/z* = 426 [M-71]); and labeled LTG (*m/z* = 431 [M-71]). A standard curve ranging from 0.25 to 20 µg/mL in unlabeled LTG concentrations and 0.025 to 2 µg/mL in labeled LTG concentrations was established, and the assay was validated in our laboratory by weighted linear regression ($1/x^2$) of the peak-area ratios (analyte peak area/internal standard peak area). LTG-IR and LTG-XR samples of each subject were extracted on the same day and compared against the same triplicate standard curve. Quality controls (QCs) for LTG were 0.75 (low), 7.5 (medium) and 16 µg/mL (high) and for LTG-SL were 0.075 (low), 0.75 (medium) and 1.6 µg/mL (high). QCs were run at

least in triplicate with each batch of plasma sample analysis. Values of QC samples were considered acceptable if the accuracy (%bias) was within ± 15% and precision (% CV) was <15% (23).

5.2.5 Study endpoints

The primary objectives of the study were 1) to assess the relative bioavailability of LTG-XR compared to LTG-IR, 2) to determine the absolute oral bioavailability for both the formulations, and 3) to characterize the elimination of LTG in elderly patients under steady-state conditions. Steady-state area under the concentration-time curve from 0 to 24 h ($AUC_{0\text{-}24,\ ss}$), maximum observed plasma concentration ($Cmax_{ss}$) and trough concentration ($C\tau_{ss}$) for unlabeled LTG, and percent absolute oral bioavailability ($\%F_{abs}$) and clearance (CL) calculated from the LTG-SL concentration-time data were considered as primary end points. Time to maximum concentration ($Tmax_{ss}$), degree of fluctuation, lowest observed concentration ($Cmin_{ss}$) and arithmetic average of steady-state plasma concentration ($Cavg_{ss}$) of LTG oral formulations were considered as secondary end points.

5.2.6 Pharmacokinetic and statistical analysis

5.2.6.1 Oral pharmacokinetics

Individual subject plasma concentration versus time data of oral LTG was subjected to non-compartmental PK analysis. The following steady state PK parameters were calculated for each subject, who were either on oral LTG-IR or LTG-XR: $AUC_{0\text{-}24\ h,\ ss}$, $Cmax_{ss}$, $Cmin_{ss}$, $Cavg_{ss}$, $C\tau_{ss}$, $Tmax_{ss}$, and fluctuation index, where fluctuation index was derived as $((Cmax_{ss} - Cmin_{ss})/Cavg_{ss} \times 100)$. Summary statistics (arithmetic and geometric mean, 95% confidence interval [CI], between-subject coefficient of variation [%CVb], standard deviation, median, and range) were calculated by regimen (LTG-XR or LTG-IR) for all PK end points. Presentations included geometric mean with its 95% CI and %CVb for all the PK parameters, except for $Tmax_{ss}$. For $Tmax_{ss}$ geometric mean and range were presented.

5.2.6.2 Relative bioavailability (LTG-XR *vs.* LTG-IR)

To assess the relative bioavailability of LTG-XR compared to LTG-IR, a dose-normalized statistical analysis was performed for both the primary endpoints and the secondary endpoints. The analysis was performed by an analysis of variance (ANOVA) appropriate for data from a classic two-period, crossover study design. The PK endpoints were dose normalized and $\log_e$ transformed in order to fit a mixed model separately for each end point, with subject as a random component, to account for the within-subject variability of the measurements. The relative bioavailability of LTG-XR to LTG-IR was assessed by utilizing the 90% confidence interval criterion (24).

5.2.6.3 Intravenous pharmacokinetics

Individual subject plasma concentration-time data of *i.v.* LTG-SL were also subjected to non-compartmental PK analysis. The following single dose *i.v.* PK parameters were calculated for each subject by treatment phase: area under the concentration-time curve from 0 to t (AUC_{0-t}), area under the concentration-time curve from 0 to infinity ($AUC_{0-\infty}$), first-order elimination rate constant (λ_z), elimination half-life ($t_{1/2}$), clearance from plasma (CL) and volume of distribution (V_z). λ_z was determined from the slope of the terminal log-linear portion of the concentration-time curve, and $t_{1/2}$ was calculated as ln2/ λ_z. AUC_{0-t} was calculated according to the linear trapezoidal rule from time 0 to the time of last quantifiable concentration after drug administration. $AUC_{0-\infty}$ was calculated as $AUC_{0-t} + C_t/ \lambda_z$ where C_t is the last quantifiable PK concentration. All PK parameters were summarized by descriptive statistics such as arithmetic means with standard deviations and geometric mean with its 95% CI and %CVb so the results could be interpreted in relation to both normal distribution and a log normal distribution.

5.2.6.4 Absolute oral bioavailability

The $\%F_{abs}$ of IR and XR formulations were calculated by the following equation and the results were presented as arithmetic mean with its standard deviation.

$$\%F_{abs} = \frac{AUC_{0-\tau,ss,oral}}{AUC_{0-\infty,iv}} \times \frac{Dose_{iv}}{Dose_{oral}} \times 100$$

The entire PK and statistical analyses were performed with Pheonix™ WinNonlin version 6.1 (Pharsight Corporation, Mountain View, CA, U.S.A.). A paired *t* test comparison with the R statistics software (version 2.11.1) (25) was performed for comparisons of $\%F_{abs}$ between IR and XR formulations and CL of LTG-SL after IR and XR treatment phases. A *p*-value < 0.05 was considered significant.

5.3 RESULTS

5.3.1 Subjects

Twelve elderly subjects (7 female, 5 male) with epilepsy (71.3 ± 7.6 years; range: 63-87 years) were enrolled in the study. The majority of the subjects (n=8) were non-Hispanic whites (67%). At the start of the study, the subjects were on a median daily dose of 250 mg of LTG-IR (range: 200-700 mg). Six subjects were on 200 mg daily dose. Ten subjects were on once daily dosing regimen and the remaining two subjects were on a twice daily dosing regimen. No subject withdrew from the study during both the treatment phases (IR and XR).

5.3.2 Oral pharmacokinetics

The median concentrations of LTG in plasma and their fluctuation window over a 24 h dosing interval were markedly lower following extended-release LTG formulation (LAMICTAL® XR™, GSK) administration compared to immediate release LTG formulation (LAMICTAL®, GSK) administration (Figure 5.2). Morning trough concentrations of LTG on the study day following LTG-XR administration for a minimum of one week were comparable to morning trough concentrations following LTG-IR administration (Figure 5.2). This observation suggests that the LTG concentrations following LTG-XR administration had reached steady-state within a week.

A summary of steady-state oral PK parameters (including their dose-normalized parameter values) for both the formulations are presented in Table 5.1. $Cmax_{ss}$ was lower in the XR treatment phase (geometric mean: 7.93 µg/mL), relative to the IR treatment phase (geometric mean: 9.36 µg/mL). Following the administration of LTG-IR, the median $Tmax_{ss}$ was 1.25 h postdose, whereas, after LTG-XR administration, $Tmax_{ss}$ was extended to 3 h postdose. The degree of fluctuation at steady state was considerably lower with LTG-XR, relative to LTG-IR (48.82% *vs.* 72.97%). Other PK parameters such as $AUC_{0\text{-}24\ h,\ ss}$, $Cmin_{ss}$, $Cavg_{ss}$ and $C\tau_{ss}$ values were similar for both the treatment phases. There was large between-subject variability for each steady-state PK parameter. This could be partly attributed to the wide range of LTG maintenance doses that subjects were receiving in the study.

5.3.3 Relative bioavailability

The results of relative bioavailability of LTG-XR compared to LTG-IR are summarized in Table 5.2. Based on the geometric least squares XR to IR mean ratios and their 90% CI, LTG-XR is similar to LTG-IR with respect to the primary endpoints, $AUC_{0\text{-}24\ h,\ ss}$ and $C\tau_{ss}$. However, $Cmax_{ss}$ of LTG-XR was on average 15% lower than for LTG-IR with 90% CI between 2% and 27% (Table 5.2). This was due to the expected lower degree of fluctuation (33% lower with 90% CI 21-43%) for LTG-XR, relative to LTG-IR. The fluctuation index (37% lower with 90% CI 24-47%) for LTG-XR was slightly improved when considered only the subjects (n=10) who were on once daily dosing schedule. $Cmin_{ss}$ and $Cavg_{ss}$ for LTG-XR were similar to LTG-IR. However, the 90% CI for $Cmin_{ss}$ (86.4-129.9%) was slightly over the confidence interval criterion (80-125%).

5.3.4 Intravenous pharmacokinetics

The intravenous infusion of LTG-SL was well tolerated with no adverse experiences and no changes in vital signs. No clinically significant changes in laboratory parameters and physical examinations occurred during the treatment phases (data on file).

The log-linear plot of mean plasma LTG-SL concentration versus time profiles following *i.v.* administration on IR and XR treatment phases were visually comparable (Figure 5.3).

The only noticeable difference was the lower exposure of LTG-SL during XR treatment phase, relative to the exposure on IR treatment phase. However, the terminal phases of LTG-SL on both the treatment phases were closely parallel to each other. Table 5.3 summarizes the PK parameters determined following *i.v.* administration of LTG-SL on each treatment phase. The PK data for the stable isotope *i.v.* formulation allowed us to characterize the clearance and volume of distribution of LTG in elderly patients. Overall the parameters were comparable between the two treatment phases, with the exception of CL, which is on the average higher for XR treatment phase compared to IR treatment phase (Table 5.3). This was partly due to more than a two fold difference in CL between two treatment phases for one of the subjects in the study. Geometric mean of $t_{1/2}$ was ~ 36 h and 32 h on IR and XR treatment phases, respectively. Geometric mean of V_z was 66 L and 74 L on IR and XR treatment phases, respectively. There was considerable between-subject variability in the PK parameter values (Table 5.3).

5.3.5 Absolute oral bioavailability

Simultaneous administration of *i.v.* LTG-SL with oral LTG allowed us to determine the $\%F_{abs}$, which was calculated to be ~ 73% for LTG-IR and ~ 92% for LTG-XR.

5.4 DISCUSSION

The steady-state pharmacokinetics were compared between LTG-IR and LTG-XR formulations in this classic two-period, crossover bioavailability study of 12 elderly subjects with epilepsy. This is the first study that reported LTG elimination characteristics as well as relative and absolute bioavailability for the formulations in elderly patients by utilizing stable isotope methodology.

The study demonstrated the comparable bioequivalence between IR and XR formulations in terms of $AUC_{0\text{-}24\ h,\ ss}$, $C\tau_{ss}$ and $Cavg_{ss}$ since the confidence intervals were within the criterion of 80-125% (24) (Table 5.2). The $\%F_{abs}$ was not statistically different between the formulations (IR: 73% ± 16% *vs.* XR: 92% ± 28%, *p*-value: 0.09). The study demonstrated 33% lower fluctuation of steady-state concentrations with LTG-XR, relative to LTG-IR. A smaller fluctuation between peak and trough concentrations with

LTG-XR may improve the tolerability and seizure control in some patients, especially those with shorter LTG half-lives or in patients taking concomitant AEDs that are known to induce LTG metabolism such as carbamazepine and phenytoin (26,27).

A slower absorption rate for the XR formulation compared to the IR formulation was observed. Visually, this was evident from the flat nature of the plasma LTG median concentration-time profile and smaller fluctuation window for LTG-XR, compared to LTG-IR (Figure 5.2). Quantitatively, this was evident from the results: longer time taken to attain $Cmax_{ss}$ with the XR formulation than the IR formulation (2.79 h *vs.* 1.43 h), lower $Cmax_{ss}$ (15% lower with 90% CI between 2% and 17%) and slightly but not significantly higher $Cmin_{ss}$ (9% higher with 90% CI between -8% and 29%). These results were supported by the fact that the LTG-XR formulation is designed to extend the duration of release of LTG by ~12-15 h, compared to LTG-IR (19).

Before we began our study, a study report (the COMPASS study) has been published describing the LTG conversion from a twice-daily IR to a once daily XR formulation in subjects with epilepsy (20). The COMPASS study demonstrated the bioequivalence between the IR and XR formulations in terms of $AUC_{0\text{-}24\ h,\ ss}$ (100% geometric least squares XR to IR ratio with 90% CI between 88% and 114%) and $C\tau_{ss}$ (114% geometric least squares XR to IR ratio with 90% CI between 103% and 125%) in subjects either on LTG monotherapy or on combination of LTG and noninducing or noninhibiting AEDs (20). Similarly, our study demonstrated the bioequivalence in terms of $AUC_{0\text{-}24\ h,\ ss}$, $C\tau_{ss}$ and $Cavg_{ss}$ in elderly subjects with epilepsy. The geometric least squares ratio of $Cmax_{ss}$ (85% with 90% CI between 73% and 98%) in our study was consistent with the finding from the COMPASS study (89% with 90% CI between 77% and 103%). With these results, our study suggests that the elderly subjects with epilepsy may also be converted directly from LTG-IR to LTG-XR without changing the total daily dose while maintaining comparable steady-state average or steady-state trough concentrations.

Application of stable isotope methodology to relative bioavailability studies is an elegant method to simultaneously determine absolute bioavailability and other PK parameters in patients without interrupting the maintenance therapy (22). Stable isotope methodology

reduces intra patient variability by avoiding a crossover design and thereby, reduces the sample size (28). Our group and others successfully utilized the stable isotope methodology to determine PK of phenytoin (29), carbamazepine (30) and valproic acid (31). It is also important to note that labeling of a drug by deuterium may alter the drug kinetics due to a potential isotope effect upon oxidative metabolism. In contrast, compounds that are labeled with ^{13}C and ^{15}N and undergoing conjugative metabolism would not exhibit a change in their PK characteristics (32).

In this classic cross-over design study, it was not possible to stop the LTG regimen in the elderly patients as they continuously needed the therapy. The determination of relative and absolute bioavailability alongside elimination of LTG in elderly patients without disrupting the maintenance therapy could only be accomplished with the stable isotope methodology. Thus, the stable isotope methodology allowed us to determine relative bioavailablity (XR *vs.* IR), $\%F_{abs}$, CL, V_z and $t_{1/2}$ in elderly patients who were on chronic LTG monotherapy. In a previous study (33), the $\%F_{abs}$ was determined (97.6 ± 4.8%) in 8 healthy, adult volunteers who received 75 mg of LTG in a gelatin capsule or LTG intravenously formulated as the isethionate salt equivalent to 75 mg of LTG free base. However, the $\%F_{abs}$ in our study was found to be low (73 ± 16%) following LTG-IR administration in elderly patients with epilepsy.

As with absolute bioavailability, all PK parameters also had wide between-subject variability. Significant difference in CL was observed between IR and XR treatment phases (1.41 ± 0.79 *vs.* 2.03 ± 1.47; *p*-value: 0.03) after the administration of LTG-SL. This could be attributed to saturation of glucuronidation pathway due to higher LTG concentrations on IR treatment phase. However, the reported K_m value (2234 ± 774 µM) for LTG in HLM (17) is much higher than the LTG therapeutic range suggesting that saturation is unlikely on XR treatment phase. On both the IR and XR treatment phases after LTG-SL administration, the mean $t_{1/2}$ was 32-38 h, exceeding the range of 24-30 h reported in the single dose studies or after the last dose of multiple dose regimens in normal volunteers (34). Similar results were also observed with stable isotope forms of carbamazepine (30) and phenytoin (29). However, the longer $t_{1/2}$ could also be attributed to reduced metabolism in elderly *vs.* young subjects. To support this, a recent study that

compared young *vs.* old adult patients revealed that the apparent clearance of LTG in older adults was approximately 20% lower than in younger adults (35). Furthermore, a comparison PK study between young and elderly healthy volunteers found a 6.3 h longer elimination half-life and a 35 % decreased mean clearance in the elderly group (10).

In conclusion, our study demonstrates the potential benefit of LTG-XR to improve the tolerability and seizure control by the lower fluctuation of steady-state concentrations compared to LTG-IR. However, due to the long half-life of LTG (32-38 h), the fluctuation index of 73% for LTG-IR is small compared to other drugs with short half-lives. In addition, it demonstrates that the elderly patients with epilepsy may be switched directly from LTG-IR to LTG-XR without changing the total daily dose while maintaining comparable steady-state average or steady-state trough concentrations.

Table 5.1. Summary of plasma lamotrigine steady-state pharmacokinetic parameters of LTG-IR and LTG-XR formulations

PK parameter (units)[a]	LTG-IR (n=12)		LTG-XR (n=12)	
	Geometric mean (95% CI)	%CVb	Geometric mean (95% CI)	%CVb
$AUC_{0\text{-}24\ h,\ ss}$ (µg.h/mL)	142.80 (92.39, 220.71)	67.90	132.34 (88.10, 198.81)	54.40
$Cmax_{ss}$ (µg/mL)	9.36 (6.14, 14.26)	57.30	7.93 (5.01, 12.54)	51.60
$Cmin_{ss}$ (µg/mL)	4.41 (2.82, 6.90)	62.60	4.81 (3.03, 7.63)	59.20
$Cavg_{ss}$ (µg/mL)	6.50 (4.25, 9.96)	59.80	6.13 (3.95, 9.53)	55.70
$C\tau_{ss}$ (µg/mL)	5.50 (3.29, 9.21)	61.80	5.58 (3.64, 8.54)	56.20
Fluctuation index (%)	72.97 (60.09, 88.62)	34.10	48.82 (40.21, 59.28)	28.00
$Tmax_{ss}$ (h)[b]	1.43 (0.00 – 4.00)		2.79 (0.00 – 8.00)	
Absolute bioavailability ($\%F_{abs}$)[c]*	73.12 ± 16.26		91.72 ± 28.08	
PK parameters normalized to 200 mg daily dose				
$AUC_{0\text{-}24\ h,\ ss,\ norm}$(µg.h/mL)	112.40 (79.32, 159.22)	43.90	104.15 (75.48, 143.71)	34.90
$Cmax_{ss,\ norm}$ (µg/mL)	7.36 (5.22, 10.39)	41.00	6.24 (4.16, 9.36)	44.70
$Cmin_{ss,\ norm}$ (µg/mL)	3.47 (2.34, 5.15)	44.80	3.78 (2.55, 5.61)	43.30
$Cavg_{ss,\ norm}$ (µg/mL)	5.12 (3.63, 7.22)	37.90	4.83 (3.32, 7.01)	43.90
$C\tau_{ss,\ norm}$ (µg/mL)	3.90 (2.22, 6.86)	68.80	4.87 (3.29, 7.22)	59.20

[a] Parameters are derived from 24 h interval data following LTG administration on the study day of each treatment phase, except for two subjects 12 h interval data was considered as they were on twice-daily dosing regimen; [b] $Tmax_{ss}$ is presented as geometric mean (n=11) and range; [c] Absolute bioavailability is presented as mean ± SD; *p = 0.09

Table 5.2. Summary of relative bioavailability statistical analysis (90% CI criterion: 80-125%) of dose-normalized steady state lamotrigine pharmacokinetic parameters (XR *vs.* IR)

PK parameter	Geometric least squares XR to IR mean ratio (%)	90% CI
$AUC_{0\text{-}24\ h,\ ss}$	92.67	(81.24, 105.71)
$Cmax_{ss}$	84.73	(73.16, 98.13)
$C\tau_{ss}$	101.32	(86.36, 118.86)
$Cmin_{ss}$	108.96	(91.89, 129.21)
$Cavg_{ss}$	94.36	(83.44, 106.70)
Fluctuation index[a]	66.90	(56.75, 78.87)

[a] fluctuation index is not a dose-normalized metric

Table 5.3. Summary of stable isotope labeled lamotrigine (LTG-SL) pharmacokinetic parameters after intravenous administration on IR and XR treatment phases

PK parameter (units)	IR treatment phase (n=12)			XR treatment phase (n=12)		
	Mean ± SD	Geometric mean (95% CI)	%CVb	Mean ± SD	Geometric mean (95% CI)	%CVb
AUC_{0-t} (µg.h/mL)	35.73 ± 14.10	32.48 (23.68, 44.55)	39.50	29.55 ± 13.86	25.37 (16.80, 38.33)	47.00
$AUC_{0-\infty}$ (µg.h/mL)	42.47 ± 15.13	39.32 (29.67, 52.12)	35.60	33.45 ± 14.50	29.52 (20.43, 42.65)	43.30
λ_z (1/h)	0.020 ± 0.006	0.019 (0.015, 0.024)	28.80	0.024 ± 0.006	0.023 (0.019, 0.027)	27.30
$t_{1/2}$ (h)	38.33 ± 16.34	35.92 (28.69, 44.97)	42.60	31.55 ± 9.47	30.36 (25.34, 36.38)	30.00
CL (L/h)*	1.41 ± 0.79	1.27 (0.96, 1.68)	55.80	2.03 ± 1.47	1.69 (1.17, 2.45)	72.20
V_z (L)	77.92 ± 52.61	65.89 (45.70, 94.99)	67.50	96.61 ± 94.06	74.20 (48.15, 114.34)	97.40

*p = 0.03

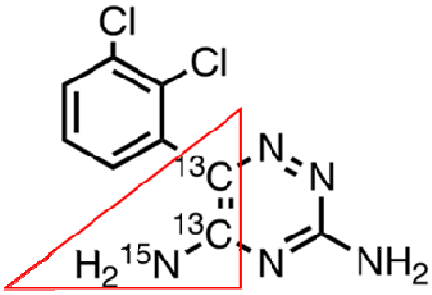

Figure 5.1. Chemical structure of LTG-SL ([$^{13}C_2$, ^{15}N]- 3, 5 diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine). Triangle shows the hotspot of the isotope labeling.

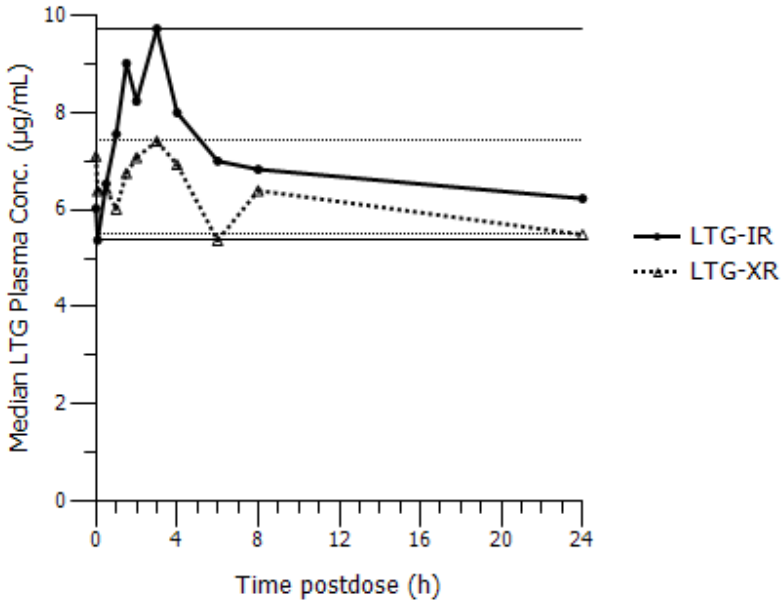

Figure 5.2. Median plasma LTG concentration *vs*. time profiles following administration of LTG-IR and LTG-XR formulations under steady-state conditions. Horizontal solid and dotted parallel straight lines represent the window of fluctuation of median LTG plasma concentrations following administration of LTG-IR and LTG-XR formulations, respectively.

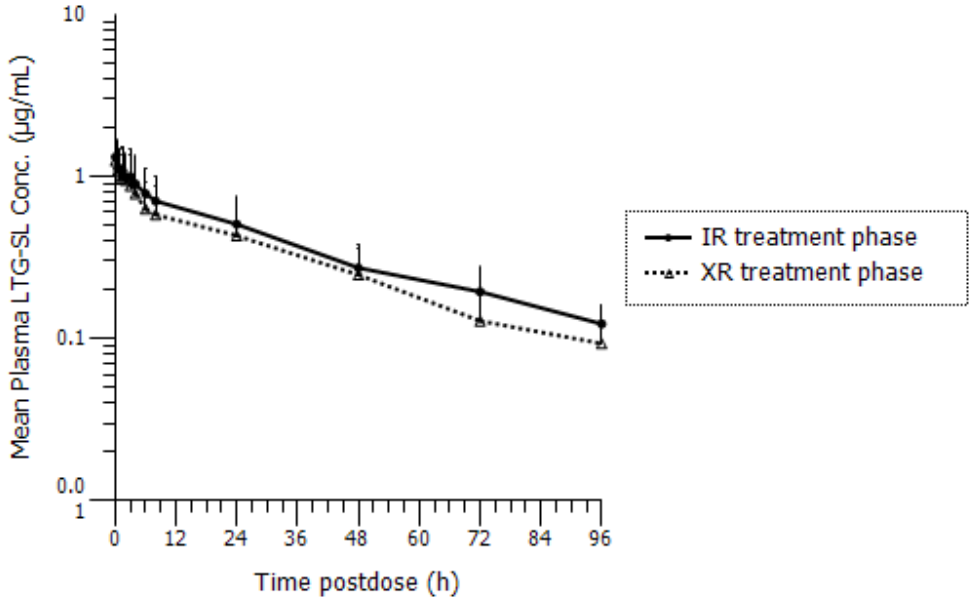

Figure 5.3. Arithmetic mean plasma concentration *vs.* time post-dose profiles following *i.v.* administration of stable labeled LTG on IR and XR treatment phases (log-linear plot). Data are shown as mean with standard deviation (upper error bar) for 12 subjects on both treatment phases (IR and XR).

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CHAPTER 6

SUMMARY & CONCLUSIONS

6.0 SUMMARY & CONCLUSIONS

The overall goal of this research work was to characterize lamotrigine (LTG) pharmacokinetics (PK) to create evidence-based guidelines for dosing of LTG in special populations. The PK of LTG has been well characterized in adult healthy volunteers and patients with epilepsy. However, two populations that are understudied are pregnant women and the elderly. Both pregnancy (1–10) and advanced age (11,12) are expected to result in changes in the PK of LTG which may result in potential loss of efficacy or safety. The need to maintain patients on steady concentrations of antiepileptic drugs (AEDs) presents another challenge in studying pharmacokinetics in epilepsy patients as discontinuing therapy in order to study AED PK is not an option. This thesis used pharmacokinetic tools, population pharmacokinetics and the creation of an intravenous stable labeled formulation of LTG, to study pharmacokinetics of LTG in pregnant women and elderly community-dwelling epilepsy patients.

Pregnant Women

Changes in LTG clearance throughout and after pregnancy are of clinical importance as they necessitate continuous monitoring and dosage adjustment during pregnancy and after delivery. The availability of LTG pharmacokinetic information in pregnant women could enable informed dosing escalation during pregnancy, reduce the amount of monitoring and clinic visits, minimize the likelihood of uncontrolled seizures and improve tolerability. We quantified the changes in LTG apparent clearance (CL/F) in pregnant women who were maintained on LTG monotherapy. We found that the CL/F of LTG was significantly influenced by gestational age and postpartum weeks. During pregnancy, we identified two subpopulations of women that exhibited different rates of increase in LTG CL/F. The LTG CL/F for a majority of the pregnant women (72%) increased by an average of 67%, 156% and 223% by the end of trimester 1, 2 and 3, respectively. The gestational age-associated increase in CL/F displayed a ten-fold higher rate (per week) in subpopulation I compared to subpopulation II. Such drastic changes in CL/F would require frequent dosage adjustments in subpopulation I. For instance, we calculated that a representative woman from subpopulation I would need approximately a 22% increase in her LTG dose at gestational week 4 when such an adjustment of dose

would be required only at the end of the third trimester for a woman from subpopulation II. Further investigations revealed heterogeneity in the racial mix between the two subpopulations with a larger prevalence of Caucasians (80%) in population I than in population II. We anticipate that race-associated genotypic variations in the activity or induction of UGT1A4 could partly explain the varying degrees of enhanced CL/F between the two groups of pregnant women and may warrant further investigation. In the postpartum period, we calculated that an average duration of 3 weeks is required for LTG CL/F to reach preconception values, and that clinicians may need to taper the dose of LTG to the baseline prescribed dose within that time interval. We recommend future studies to investigate the underlying reasons for varying rates of enhanced LTG CL/F during pregnancy and to explore possible race-linked polymorphisms in UGT1A4 or estrogen receptor.

Despite the substantial variability in the CL/F of LTG during pregnancy, we found that therapeutic drug monitoring was effective in controlling seizures. We reported a low rate of seizures (0.04 seizures/week) and found that 69% of our observations reflected no seizures observed (zero count). We were unable to further explore the predictors of seizures in pregnant women as the collected seizure count data were not sufficient for this analysis. Future studies are needed to better understand the seizure frequencies in pregnant women. These studies should include a larger sample size of pregnant women with epilepsy in order to maintain the statistical power needed for analysis of seizure frequencies. In addition, studies with seizures observed over uniform time intervals (i.e., uniform resolution) over the course of pregnancy are useful for easy implementation of seizure count models.

Elderly Patients with Epilepsy

With the creation of a stable-labeled intravenous LTG formulation we were able to administer LTG by two routes (i.e., oral and intravenous) simultaneously in younger adults and elderly patients with epilepsy. This enabled us to determine absolute bioavailability (*F*), clearance (CL), volume of distribution, and elimination half-life under steady-state conditions without disrupting the LTG therapy in the patients. Most

importantly, intravenous stable labeled LTG allowed the estimation of *F* and the exploration of an age effect on LTG CL while excluding variability in absorption. For the first time, we reported *F* (75%) of LTG tablets in patients and found that it did not differ between young and elderly patients. After accounting for body weight, CL was 27% lower on average for elderly patients compared to younger adults. This result may support a dose adjustment based on age where an elderly patient would receive, on average, 73% of the dose prescribed for a younger adult. In addition, the study reported a nine hour longer terminal half-life in elderly patients compared to younger adults. Inclusion of body weight of the patients explained much of the variability in central volume of distribution and intercompartmental clearance. We hypothesized that the observed reduction in CL may be caused by a reduced enzyme capacity (or UGT1A4 expression) and/or liver volume in the elderly group (13,14). Therefore, we recommend future studies to investigate age-selective differences in UGT1A4 expression. These studies could provide more information on the pharmacological basis of differences in CL between young and elderly patients.

Our studies also included investigation of two LTG formulations in the elderly patients. We demonstrated a comparable bioequivalence between XR and IR formulations in terms of steady-state area under the concentration-time curve, trough concentration and average of steady-state plasma concentration through a classic two-period, crossover bioavailability study. These results suggest that elderly patients with epilepsy may be converted directly from IR to XR without changing the total daily dose in order to maintain comparable steady-state average or trough concentrations. In addition, the data showed a 33% lower fluctuation of peak-to-trough concentrations with XR, relative to IR. Lower fluctuations during a dosing interval could result in improved tolerability and seizure control in the elderly patients by maintaining patients at more steady blood concentrations. The *F* of XR and IR LTG formulations were estimated to be 92% and 73%, respectively.

Conclusions

In conclusion, we characterized LTG PK in different populations of epilepsy patients including pregnant women, younger adults and elderly patients by utilizing pharmacometric analysis approaches. In pregnant women, we found that the LTG CL/F significantly increased during pregnancy and reached baseline within 3 weeks after delivery. In addition, we identified two subpopulations of women that exhibited varying degrees of enhanced CL/F during pregnancy. This finding warrants future studies to investigate genotypic variations in the activity or inducibility of UGT1A4 as well as polymorphisms associated with estrogen receptor. When exploring seizure frequencies in pregnant women, the seizure rate was low most likely due to effective therapeutic drug monitoring. Future studies with a larger number of patients may provide information on exposure-response and time course changes of seizures in pregnant women. When comparing the elderly with younger adult patients, we found age-related changes in LTG PK. In the elderly, the LTG CL was lower and terminal half-life was longer compared to younger adult patients. Further studies which investigate UGT1A4 expression in the elderly may provide more information on the reduced CL. Comparison of XR *vs.* IR revealed that the elderly patients may be switched directly from IR to XR without changing the total daily dose, and the XR may improve tolerability and seizure control compared to IR.

Overall, the studies presented in this thesis characterized the LTG PK in special populations that are underrepresented in clinical studies. We were unable to fully explain some of the PK findings in pregnant women or the elderly due to the lack of information on UGT1A4 genotypes. Therefore, future studies of LTG in these populations should investigate genotypic variations and expression of the main metabolic enzyme UGT1A4.

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APPENDIX

A. NONMEM Code for Characterization of Changes in Lamotrigine Clearance during Pregnancy (Chapter 2)

```
;Model Desc: LTG CL mixture model
;Project Name: ltg_preg
;Project ID: LTG_PREG_001

$PROB RUN# 108del_mix_slope
$INPUT C RWID=DROP ID PTID=DROP SAMT=DROP DATE=DROP
DOSE=DROP RATE CTIM=DROP TAD DV FDV=DROP RACE ETHN AGE HT
PCWT=DROP WT CHWT=DROP PBMI=DROP BMI CBMI=DROP EGA PP
DAY=DROP TM STR=DROP DLRY
$DATA SSDATASET10102010.CSV IGNORE=C

$PRED
EST=MIXEST
GA=EGA
DELW=EGA-PP

IF(TM.EQ.0) GA=0
TVBL=THETA(1)
BL=TVBL*EXP(ETA(1))

IF(MIXNUM.EQ.1) THEN
IF(TM.GT.0.AND.TM.LT.4) THEN
IBL=THETA(2)*GA
ELSE
IBL=THETA(2)*DELW
ENDIF
ELSE
IF(TM.GT.0.AND.TM.LT.4) THEN
IBL=THETA(3)*GA
ELSE
IBL=THETA(3)*DELW
ENDIF
ENDIF

IF(TM.EQ.0) THEN
CBL=0
ELSE
CBL=IBL*EXP(ETA(2))
ENDIF

CL1=BL+CBL
```

```
IF(TM.LT.4) THEN
CL=CL1
ELSE
CL=CBL*EXP(-THETA(4)*PP)+BL
ENDIF

CONC=RATE/CL

Y = CONC + CONC*ERR(1)
IPRE=CONC
DELBL=BL-TVBL
DELCBL=CBL-IBL

$MIX
NSPOP=2
P(1)=THETA(5)
P(2)=1-P(1)

$COV
$THETA
(0,2)          ;[BLCL]
(0,0.05)       ;[SLOPE1]
(0,0.05)       ;[SLOPE2]
(0,0.33)       ;[DECAY]
(0,0.3)        ;[PROB]

$OMEGA
0.1            ;[P] omega(1,1)
0.2            ;[P] omega(2,2)
$SIGMA
0.1            ;[P] sigma(1,1)

$EST PRINT=5 MAX=9999 SIG=3 METH=1 INTERACTION
MSFO=108del_mix_slope.MSF

$TABLE ID TAD CL WT EGA GA PP DELW TM BL IBL CBL CL1 CL IPRE DELBL
DELCBL AGE HT BMI RACE ETHN ETA1 ETA2 EST CWRES ONEHEADER
NOPRINT FILE=108del_mix_slope.tab
```

B. NONMEM Code for Modeling Seizure Counts: Poisson Model (Chapter 3)

```
;Model Desc: Poisson_model
;Project Name: ltg_pd3
;Project ID: NO PROJECT DESCRIPTION

$PROB SZ_COUNT MODEL
$INPUT C ID PTID=DROP PD CUM COUNT=DV TDUR DOSE RATE CONC GA PP
TM DLRY DELW BL CL RACE ETHN AGE=DROP HT PCWT WT=DROP
CHWT=DROP PBMI BMI=DROP CBMI=DROP
$DATA PD_exposure_dataset_n_39_01202012.csv IGNORE=C IGNORE=(CUM=0)

$PRED
TLAM=THETA(1)
LAM=TLAM+ETA(1)
TLLM=LOG(TDUR)+TLAM          ;Typical value of log(lambda)
LLM=LOG(TDUR)+LAM    ;Log(lambda) with interindividual variability
LM=DEXP(LLM)                 ;Lambda with IIV
TLM=DEXP(TLLM)               ;Population Lambda (For table)

;#########################################################################
;#LIKELIHOOD
;FACT =1
;IF (DV.GT.0) FACT=SQRT(2*3.1415)*(DV**(DV+0.5))*EXP(-DV)*(1+1/(12*DV))

;#Poisson Distribution
;POIS=(LM**DV)*DEXP(-LM)/FACT

;#Typical value of Poisson
;#(coded for inclusion in table)
;#(gives probability based on population mean)

;TPOIS=(TLM**DV)*DEXP(-TLM)/FACT
;Y=POIS
;#########################################################################
;#-2LOGLIKELIHOOD

LFACT = 0
IF (DV.GT.0) LFACT= LOG(SQRT(2*3.1415))+(DV+0.5)*LOG(DV)-
DV+LOG(1+1/(12*DV))
POIS=DV*LOG(LM)-LM-LFACT
TPOIS=DV*LOG(TLM)-TLM-LFACT       ;population based probability for table

Y=-2*POIS
;#########################################################################
```

```
IPRE=LM
PRE=TLM

PROB=DEXP(POIS)          ;probability for table
TPROB=DEXP(TPOIS)        ;population based probability for table

$THETA
1        ;[TLLAM]
$OMEGA
0.01     ;[A] omega(1,1)

$ESTM NOABORT PRINT=5 MAXEVAL=9999 METHOD=1 LAPLACE -2LL
MSFO=5a_Poission_offset_-2LL_reparam.MSF

$COV

$TABLE ID PD CUM COUNT TDUR DOSE RATE CONC GA PP TM DLRY BL CL
RACE ETHN  HT PCWT PBMI LFACT POIS TPOIS IPRE PRE PROB TPROB
CWRES ONEHEADER NOPRINT FILE=5a_Poission_offset_-2LL_reparam.tab
```

C. NONMEM Code for Modeling Seizure Counts: Zero-Inflated Poisson (ZIP) Model (Chapter 3)

```
;Model Desc: ZIP Model
;Project Name: ltg_pd3
;Project ID: NO PROJECT DESCRIPTION

$PROB SZ_COUNT MODEL
$INPUT C ID PTID=DROP PD CUM COUNT=DV TDUR DOSE RATE CONC GA PP
TM DLRY DELW BL CL RACE ETHN AGE=DROP HT PCWT WT=DROP
CHWT=DROP PBMI BMI=DROP CBMI=DROP
$DATA PD_exposure_dataset_n_39_01202012.csv IGNORE=C IGNORE=(CUM=0)

$PRED
TLAM=THETA(1)
LAM=TLAM+ETA(1)
TLLM=LOG(TDUR)+TLAM          ;Typical value of log(lambda)
LLM=LOG(TDUR)+LAM            ;Log(lambda) with interindividual variability
LM=DEXP(LLM)                 ;Lambda with IIV
TLM=DEXP(TLLM)               ;Population Lambda (For table)

TLOGIT = THETA(2)                              ;Typical value of the logit
TPHI=DEXP(TLOGIT)/(1+DEXP(TLOGIT))  ;typical value of probability (for table)
LOGIT = TLOGIT+ETA(2)                          ;Add intersubject variability
PHI = DEXP(LOGIT)/(1+DEXP(LOGIT))              ;subject level probability
PPHI = DEXP(TLOGIT)/(1+DEXP(TLOGIT))          ;population level probability

;#########################################################################
;#LIKELIHOOD
FACT =1
IF (DV.GT.0) FACT=SQRT(2*3.1415)*(DV**(DV+0.5))*EXP(-DV)*(1+1/(12*DV))

;#Poisson Distribution
POIS=(LM**DV)*DEXP(-LM)/FACT

;#Typical value of Poisson
;#(coded for inclusion in table)
;#(gives probability based on population mean)
TPOIS=(TLM**DV)*DEXP(-TLM)/FACT
;#########################################################################
STATE=0
IF (DV.EQ.0) STATE=1
P0=PHI + (1-PHI)*DEXP(-LM)       ;Probability of zero count
PN=(1-PHI)*POIS                  ;Probability of count 1,2,3,. . .
ZIP=P0**STATE * PN**(1-STATE)          ;
Y=ZIP
```

```
STATE=0
IF (DV.EQ.0) STATE=1
TP0=TPHI + (1-TPHI)*DEXP(-TLM)        ;Probability of zero count
TPN=(1-TPHI)*TPOIS                    ;Probability of count 1,2,3,. . .
TZIP=TP0**STATE * TPN**(1-STATE)      ;

;for table
EYI=(1-PHI)*LM                  ;Subject-level expectation
VYI=EYI+EYI*(LM-EYI)            ;Subject-level variance of count
EYP=(1-PPHI)*TLM                ;Population expectation
VYP=EYP+EYP*(TLM-EYP)           ;Population variance of count
;#########################################################################
IPRE=LM
PRE=TLM

PROB=POIS               ;subject level probability for table
TPROB=TPOIS             ;population based probability for table
ZPROB=ZIP               ;probability
TZPROB=TZIP             ;probability


$THETA
1       ;[TLLAM]
1       ;[TLOG]
$OMEGA
0.01    ;[A] omega(1,1)
0.01    ;[A] omega(2,2)

$ESTM NOABORT PRINT=5 MAXEVAL=9999 METHOD=1 LAPLACE
LIKELIHOOD

$COV

$TABLE ID PD CUM COUNT TDUR DOSE RATE CONC GA PP TM DLRY BL CL
RACE ETHN  HT PCWT PBMI POIS TPOIS IPRE PRE PROB TPROB TZPROB
ZPROB LOGIT TLOGIT PHI TPHI PPHI ZIP CWRES ONEHEADER NOPRINT
FILE=7_ZIP_offset_Likelihood_reparam.tab
```

D. NONMEM Code for Modeling Seizure Counts: Hurdle (HDL) Model (Chapter 3)

```
;Model Desc: HDL model
;Project Name: ltg_pd3
;Project ID: NO PROJECT DESCRIPTION

$PROB SZ_COUNT MODEL
$INPUT C ID PTID=DROP PD CUM COUNT=DV TDUR DOSE RATE CONC GA PP
TM DLRY DELW BL CL RACE ETHN AGE=DROP HT PCWT WT=DROP
CHWT=DROP PBMI BMI=DROP CBMI=DROP
$DATA PD_exposure_dataset_n_39_01202012.csv IGNORE=C IGNORE=(CUM=0)

$PRED
TLAM=THETA(1)
LAM=TLAM+ETA(1)
TLLM=LOG(TDUR)+TLAM          ;Typical value of log(lambda)
LLM=LOG(TDUR)+LAM            ;Log(lambda) with interindividual variability
LM=DEXP(LLM)                 ;Lambda with IIV
TLM=DEXP(TLLM)               ;Population Lambda (For table)

TLOGIT = THETA(2)                              ;Typical value of the logit
TPHI=DEXP(TLOGIT)/(1+DEXP(TLOGIT)) ;typical value of probability (for table)
LOGIT = TLOGIT + ETA(2)                        ;Add intersubject variability
PHI = DEXP(LOGIT)/(1+DEXP(LOGIT))              ;subject level probability
PPHI = DEXP(TLOGIT)/(1+DEXP(TLOGIT))          ;population level probability
;#########################################################################
;#LIKELIHOOD
FACT =1
IF (DV.GT.0) FACT=SQRT(2*3.1415)*(DV**(DV+0.5))*EXP(-DV)*(1+1/(12*DV))

;#Poisson Distribution
POIS=(LM**DV)*DEXP(-LM)/FACT


;#Typical value of Poisson
;#(coded for inclusion in table)
;#(gives probability based on population mean)

TPOIS=(TLM**DV)*DEXP(-TLM)/FACT
;#########################################################################
STATE=0
IF (DV.EQ.0) STATE=1
P0=PHI                                ;Probability of zero count
PN=(1-PHI)*POIS/(1-DEXP(-LM))  ;Probability of count 1,2,3,. . .
HDL=P0**STATE * PN**(1-STATE)         ;
```

```
Y=HDL

STATE=0
IF (DV.EQ.0) STATE=1
TP0=TPHI                                    ;Probability of zero count
TPN=(1-TPHI)*TPOIS/(1-DEXP(-TLM))   ;Probability of count 1,2,3,. . .
THDL=TP0**STATE * TPN**(1-STATE)  ;
;#####################################################################

IPRE=LM
PRE=TLM

PROB=POIS           ;subject level probability for table
TPROB=TPOIS         ;population based probability for table
ZPROB=HDL           ;probability
TZPROB=THDL         ;probability

$THETA
1       ;[TLLAM]
1       ;[TLOGIT]
$OMEGA
0.01    ;[A] OMEGA(1,1)
0.01    ;[A] OMEGA(2,2)

$ESTM NOABORT PRINT=5 MAXEVAL=9999 METHOD=1 LAPLACE
LIKELIHOOD

$COV

$TABLE ID PD CUM COUNT TDUR DOSE RATE CONC GA PP TM DLRY BL CL
RACE ETHN  HT PCWT PBMI POIS TPOIS IPRE PRE PROB TPROB TZPROB
ZPROB LOGIT TLOGIT PHI TPHI PPHI HDL CWRES ONEHEADER NOPRINT
FILE=10_Hurdle_offset_like_reparam.tab
```

E. NONMEM Code for Modeling Seizure Counts: Negative Binomial (NB) Model _ FINAL MODEL (Chapter 3)

```
;Model Desc: NB model
;Project Name: ltg_pd3
;Project ID: NO PROJECT DESCRIPTION

$PROB SZ_COUNT MODEL
$INPUT C ID PTID=DROP PD CUM COUNT=DV TDUR DOSE RATE CONC GA PP
TM DLRY DELW BL CL RACE ETHN AGE=DROP HT PCWT WT=DROP
CHWT=DROP PBMI BMI=DROP CBMI=DROP
$DATA PD_exposure_dataset_n_39_01202012.csv IGNORE=C IGNORE=(CUM=0)

$PRED
TLAM=THETA(1)
LAM=TLAM + ETA(1)
LLM=LOG(TDUR)+LAM          ;Typical value of log(lambda)
TLLM=LOG(TDUR)+TLAM        ;Log(lambda) with interindividual variability
LM=DEXP(LLM)               ;Lambda with IIV
TLM=DEXP(TLLM)             ;Population Lambda (For table)

TOVDP = THETA(2)                ;Typical value of the OVDP
OVDP  = TOVDP ;*EXP(ETA(2))     ;Add intersubject variability

;#LIKELIHOOD
;Binomial distribution formula
AGM1 = DV+(1/OVDP)
AGM2 = 1/OVDP
TAGM1 = DV+(1/TOVDP)
TAGM2 = 1/TOVDP

;Log of gamma functions
GAM1 = SQRT(2*3.1415)*((AGM1)**((AGM1)-0.5))*EXP(-
(AGM1))*(1+1/(12*(AGM1)))

GAM2 = SQRT(2*3.1415)*((AGM2)**((AGM2)-0.5))*EXP(
(AGM2))*(1+1/(12*(AGM2)))

TGAM1 = SQRT(2*3.1415)*((TAGM1)**((TAGM1)-0.5))*EXP(
(TAGM1))*(1+1/(12*(TAGM1)))

TGAM2 = SQRT(2*3.1415)*((TAGM2)**((TAGM2)-0.5))*EXP(-
(TAGM2))*(1+1/(12*(TAGM2)))

;Parts of negative binomial formula
TRM1 = (1/(1+OVDP*LM))**(1/OVDP)
```

```
TRM2 = (LM/(LM+1/OVDP))**DV
TTRM1 = (1/(1+TOVDP*TLM))**(1/TOVDP)
TTRM2 = (TLM/(TLM+1/TOVDP))**DV

;Sterling's formula
FACT =1
IF (DV.GT.0) FACT=SQRT(2*3.1415)*(DV**(DV+0.5))*EXP(-DV)*(1+1/(12*DV))

;Log of NB distribution formula
NB = (GAM1/(FACT*GAM2))*TRM1*TRM2
TNB = (TGAM1/(FACT*TGAM2))*TTRM1*TTRM2

;Y in the form of likelihood
Y = NB

IPRE=LM
PRE=TLM

PROB=NB          ;subject level probability for table
TPROB=TNB        ;population level probability for table

$THETA
1       ;[TLLAM]
1       ;[TOVDP]
$OMEGA
0.1     ;[P] OMEGA(1,1)

$ESTM NOABORT PRINT=5 MAXEVAL=9999 METHOD=1 LAPLACE
LIKELIHOOD

$COV

$TABLE ID PD CUM COUNT TDUR DOSE RATE CONC GA PP TM DLRY BL CL
RACE ETHN  HT PCWT PBMI IPRE PRE PROB TPROB LLM TLLM LM TLM
OVDP TOVDP CWRES ONEHEADER NOPRINT FILE=8b_NB_offset_Like-
reparam.tab
```

F. NONMEM Code for Modeling Seizure Counts: Zero-Inflated Negative Binomial (ZINB) Model (Chapter 3)

```
;Model Desc: ZINB Model
;Project Name: ltg_pd3
;Project ID: NO PROJECT DESCRIPTION

$PROB SZ_COUNT MODEL
$INPUT C ID PTID=DROP PD CUM COUNT=DV TDUR DOSE RATE CONC GA PP
TM DLRY DELW BL CL RACE ETHN AGE=DROP HT PCWT WT=DROP
CHWT=DROP PBMI BMI=DROP CBMI=DROP
$DATA PD_exposure_dataset_n_39_01202012.csv IGNORE=C IGNORE=(CUM=0)

$PRED
TLAM=THETA(1)
LAM=TLAM + ETA(1)
TLLM=LOG(TDUR)+TLAM          ;Typical value of log(lambda)
LLM=LOG(TDUR)+LAM            ;Log(lambda) with interindividual variability
LM=DEXP(LLM)                 ;Lambda with IIV
TLM=DEXP(TLLM)               ;Population Lambda (For table)

TOVDP = THETA(2)                    ;Typical value of the OVDP
OVDP  = TOVDP ;*EXP(ETA(2))         ;Add intersubject variability

TLOGIT = THETA(3)                                ;Typical value of the logit
TPHI=DEXP(TLOGIT)/(1+DEXP(TLOGIT)) ;typical value of probability (for table)
LOGIT = TLOGIT ;+ ETA(3)                         ;Add intersubject variability
PHI = DEXP(LOGIT)/(1+DEXP(LOGIT))                ;subject level probability
PPHI = DEXP(TLOGIT)/(1+DEXP(TLOGIT))             ;population level probability

;#LIKELIHOOD
;Binomial distribution formula
AGM1 = DV+(1/OVDP)
AGM2 = 1/OVDP

TAGM1 = DV+(1/TOVDP)
TAGM2 = 1/TOVDP

;Log of gamma functions
GAM1 = SQRT(2*3.1415)*((AGM1)**((AGM1)-0.5))*EXP(-
(AGM1))*(1+1/(12*(AGM1)))

GAM2 = SQRT(2*3.1415)*((AGM2)**((AGM2)-0.5))*EXP(-
(AGM2))*(1+1/(12*(AGM2)))
```

```
TGAM1 = SQRT(2*3.1415)*((TAGM1)**((TAGM1)-0.5))*EXP(-
(TAGM1))*(1+1/(12*(TAGM1)))

TGAM2 = SQRT(2*3.1415)*((TAGM2)**((TAGM2)-0.5))*EXP(-
(TAGM2))*(1+1/(12*(TAGM2)))

;Parts of negative binomial formula
TRM1 = (1/(1+OVDP*LM))**(1/OVDP)
TRM2 = (LM/(LM+1/OVDP))**DV

TTRM1 = (1/(1+TOVDP*TLM))**(1/TOVDP)
TTRM2 = (TLM/(TLM+1/TOVDP))**DV

;Sterling's formula
FACT =1
IF (DV.GT.0) FACT=SQRT(2*3.1415)*(DV**(DV+0.5))*EXP(-DV)*(1+1/(12*DV))

;Log of NB distribution formula
NB = (GAM1/(FACT*GAM2))*TRM1*TRM2
TNB = (TGAM1/(FACT*TGAM2))*TTRM1*TTRM2
;#########################################################################
STATE=0
IF (DV.EQ.0) STATE=1
TP0=TPHI + (1-TPHI)*TTRM1              ;Probability of zero count
TPN=(1-TPHI)*TNB                       ;Probability of count 1,2,3,. . .
TZINB=TP0**STATE * TPN**(1-STATE)          ;

STATE=0
IF (DV.EQ.0) STATE=1
P0=PHI + (1-PHI)*TRM1              ;Probability of zero count
PN=(1-PHI)*NB                      ;Probability of count 1,2,3,. . .
ZINB=P0**STATE * PN**(1-STATE)       ;
Y=ZINB
;for table
EYI=(1-PHI)*LM                                  ;Subject-level expectation
VYI=(1-PHI)*LM*(1+PHI*LM+OVDP*LM)       ;Subject-level variance of count
EYP=(1-PPHI)*TLM                                ;Population expectation
VYP=(1-PPHI)*TLM*(1+PPHI*TLM+TOVDP*TLM)     ;Population variance of count
;#########################################################################
IPRE=LM
PRE=TLM
PROB=ZINB          ;subject level probability for table
TPROB=TZINB        ;population level probability for table

$THETA
-2       ;[TLLAM]
```

```
2        ;[TOVDP]
-20      ;[TLOGIT]

$OMEGA
0.09     ;[P] OMEGA(1,1)

$ESTM NOABORT PRINT=5 MAXEVAL=9999 METHOD=1 LAPLACE
LIKELIHOOD
$COV

$TABLE ID PD CUM COUNT TDUR DOSE RATE CONC GA PP TM DLRY BL CL
RACE ETHN  HT PCWT PBMI IPRE PRE PROB TPROB LM TLM OVDP TOVDP
EYI VYI EYP VYP  CWRES ONEHEADER NOPRINT
FILE=9b_ZINB_offset_likel_reparam.tab
```

G. NONMEM Code for Modeling Seizure Counts: Negative Binomial Model with Mixture Probability (NBMIX) (Chapter 3)

```
;Model Desc: NBMIX model
;Project Name: ltg_pd3
;Project ID: NO PROJECT DESCRIPTION

$PROB SZ_COUNT MODEL
$INPUT C ID PTID=DROP PD CUM COUNT=DV PDV TDUR DOSE RATE CONC
GA PP TM DLRY DELW BL CL RACE ETHN AGE=DROP HT PCWT WT=DROP
CHWT=DROP PBMI BMI=DROP CBMI=DROP
$DATA PD_exp_data_markov_n_39_01202012.csv IGNORE=C

$PRED
EST=MIXEST
IF(MIXNUM.EQ.1) THEN
TLAM=THETA(1)
LAM=TLAM + ETA(1)
ELSE
TLAM=THETA(2)
LAM=TLAM + ETA(2)
ENDIF

LLM=LOG(TDUR)+LAM          ;Typical value of log(lambda)
TLLM=LOG(TDUR)+TLAM        ;Log(lambda) with interindividual variability
LM=DEXP(LLM)               ;Lambda with IIV
TLM=DEXP(TLLM)             ;Population Lambda (For table)

IF(MIXNUM.EQ.1) THEN
TOVDP = THETA(3)
OVDP  = TOVDP ;*EXP(ETA(2))
ELSE
TOVDP=THETA(4)
OVDP=TOVDP ;*EXP(ETA(2))
ENDIF

;#LIKELIHOOD
;Binomial distribution formula
AGM1 = DV+(1/OVDP)
AGM2 = 1/OVDP

TAGM1 = DV+(1/TOVDP)
TAGM2 = 1/TOVDP
```

```
;gamma functions
GAM1 = SQRT(2*3.1415)*((AGM1)**((AGM1)-0.5))*EXP(-
(AGM1))*(1+1/(12*(AGM1)))

GAM2 = SQRT(2*3.1415)*((AGM2)**((AGM2)-0.5))*EXP(-
(AGM2))*(1+1/(12*(AGM2)))

TGAM1 = SQRT(2*3.1415)*((TAGM1)**((TAGM1)-0.5))*EXP(-
(TAGM1))*(1+1/(12*(TAGM1)))

TGAM2 = SQRT(2*3.1415)*((TAGM2)**((TAGM2)-0.5))*EXP(-
(TAGM2))*(1+1/(12*(TAGM2)))

;Parts of negative binomial formula
TRM1 = (1/(1+OVDP*LM))**(1/OVDP)
TRM2 = (LM/(LM+1/OVDP))**DV

TTRM1 = (1/(1+TOVDP*TLM))**(1/TOVDP)
TTRM2 = (TLM/(TLM+1/TOVDP))**DV

;Sterling's formula
FACT =1
IF (DV.GT.0) FACT=SQRT(2*3.1415)*(DV**(DV+0.5))*EXP(-DV)*(1+1/(12*DV))

;NB distribution formula
NB = (GAM1/(FACT*GAM2))*TRM1*TRM2
TNB = (TGAM1/(FACT*TGAM2))*TTRM1*TTRM2

;Y in the form of likelihood
Y = NB

IPRE=LM
PRED=TLM
PROB=NB          ;subject level probability for table
TPROB=TNB        ;population level probability for table

$MIX
NSPOP=2
P(1)=THETA(5)
P(2)=1-P(1)

$THETA
-1      ;[TLAM10]
-1      ;[TLAM20]
(0,2)   ;[TOVDP10]
(0,2)   ;[TOVDP20]
```

```
(0,0.3) ;[MIXPROB]

$OMEGA
0.1     ;[P] OMEGA(1,1)
0.1     ;[P] OMEGA(2,2)

$ESTM NOABORT PRINT=5 MAXEVAL=9999 METHOD=1 SIGDIG=5 LAPLACE
LIKELIHOOD MSFO=8b_NBMIX_offset_Like_reparam.MSF

$COV

$TABLE ID PD CUM COUNT PDV TDUR DOSE RATE CONC GA PP TM DLRY
BL CL RACE ETHN  HT PCWT PBMI IPRE PRED PROB TPROB LLM TLLM LM
TLM OVDP TOVDP CWRES EST ONEHEADER NOPRINT
FILE=8b_NBMIX_offset_Like_reparam.tab
```

H. NONMEM Code for Modeling Seizure Counts: Negative Binomial Model with Markovian Element (NBMAK) (Chapter 3)

```
;Model Desc: NBMAK model
;Project Name: ltg_pd3
;Project ID: NO PROJECT DESCRIPTION

$PROB SZ_COUNT MODEL
$INPUT C ID PTID=DROP PD CUM COUNT=DV PDV TDUR DOSE RATE CONC
GA PP TM DLRY DELW BL CL RACE ETHN AGE=DROP HT PCWT WT=DROP
CHWT=DROP PBMI BMI=DROP CBMI=DROP
$DATA PD_exp_data_markov_n_39_01202012.csv IGNORE=C

$PRED
IF(PDV.EQ.0) THEN
TLAM=THETA(1)
LAM=TLAM + ETA(1) ;*EXP(ETA(1))
ELSE
TLAM=THETA(2)
LAM=TLAM + ETA(1) ;*EXP(ETA(1))
ENDIF

LLM=LOG(TDUR)+LAM          ;Typical value of log(lambda)
TLLM=LOG(TDUR)+TLAM        ;Log(lambda) with interindividual variability
LM=DEXP(LLM)               ;Lambda with IIV
TLM=DEXP(TLLM)             ;Population Lambda (For table)

IF(PDV.EQ.0) THEN
TOVDP = THETA(3)
OVDP  = TOVDP ;*EXP(ETA(2))
ELSE
TOVDP=THETA(4)
OVDP=TOVDP ;*EXP(ETA(2))
ENDIF

;#LIKELIHOOD
;Binomial distribution formula
AGM1 = DV+(1/OVDP)
AGM2 = 1/OVDP

TAGM1 = DV+(1/TOVDP)
TAGM2 = 1/TOVDP

;gamma functions
GAM1 = SQRT(2*3.1415)*((AGM1)**((AGM1)-0.5))*EXP(-
(AGM1))*(1+1/(12*(AGM1)))
```

```
GAM2 = SQRT(2*3.1415)*((AGM2)**((AGM2)-0.5))*EXP(-
(AGM2))*(1+1/(12*(AGM2)))

TGAM1 = SQRT(2*3.1415)*((TAGM1)**((TAGM1)-0.5))*EXP(-
(TAGM1))*(1+1/(12*(TAGM1)))

TGAM2 = SQRT(2*3.1415)*((TAGM2)**((TAGM2)-0.5))*EXP(-
(TAGM2))*(1+1/(12*(TAGM2)))

;Parts of negative binomial formula
TRM1 = (1/(1+OVDP*LM))**(1/OVDP)
TRM2 = (LM/(LM+1/OVDP))**DV

TTRM1 = (1/(1+TOVDP*TLM))**(1/TOVDP)
TTRM2 = (TLM/(TLM+1/TOVDP))**DV

;Sterling's formula
FACT =1
IF (DV.GT.0) FACT=SQRT(2*3.1415)*(DV**(DV+0.5))*EXP(-DV)*(1+1/(12*DV))

;NB distribution formula
NB = (GAM1/(FACT*GAM2))*TRM1*TRM2
TNB = (TGAM1/(FACT*TGAM2))*TTRM1*TTRM2

;Y in the form of likelihood
Y = NB

IPRE=LM
PRE=TLM
PROB=NB          ;subject level probability for table
TPROB=TNB        ;population level probability for table

$THETA
-4      ;[TLAM0]
-2      ;[TLAM1]
(0,3)   ;[TOVDP0]
(0,2)   ;[TOVDP1]
$OMEGA
2       ;[A] OMEGA(1,1)
;;0.04  ;IIV on LAM2
;0.5    ;[A] OMEGA(2,2)
;0.5    ;[P] OMEGA(2,2)
;;0.04  ;IIV on OVDP2

$ESTM NOABORT PRINT=5 MAXEVAL=9999 METHOD=1 SIGDIG=5 LAPLACE
LIKELIHOOD MSFO=8b_NB_offset_Like-markov_reparam.MSF
```

```
$COV

$TABLE ID PD CUM COUNT PDV TDUR DOSE RATE CONC GA PP TM DLRY
BL CL RACE ETHN  HT PCWT PBMI IPRE PRE PROB TPROB LM TLM OVDP
TOVDP CWRES ONEHEADER NOPRINT FILE=8b_NB_offset_Like-
markov_reparam.tab
```

I. NONMEM Code for Analysis of Simultaneous Oral and Stable-Labeled Intravenous Lamotrigine Pharmacokinetics Data from Young and Elderly Epilepsy Patients (Chapter 4)

```
;Model Desc: TWO COMPT MODEL_FINAL MODEL
;Project Name: ltg_yng_eld
;Project ID: NO PROJECT DESCRIPTION

$PROB RUN# 083
$INPUT C ID SID=DROP NTIM ATIM TAD TIME DV AMT RATE MDV EVID
ADDL SS II CMT ROUTE CTR YNG AGE WT SEX RACE ETHN ETOH SMOK SCR
CRCL BUN BSR ALB AST ALT HCT

$DATA 102_08222012.CSV IGNORE=C
$SUBROUTINES ADVAN4 TRANS4

$PK
SID=ID
TVCL=THETA(1)*((WT/70)**THETA(7))*(THETA(8)**YNG)
CL=TVCL*EXP(ETA(1))
TVV2=THETA(2)*(WT/70)
V2=TVV2*EXP(ETA(2))
TVQ=THETA(3)*(WT/70)**0.75
Q=TVQ*EXP(ETA(3))
TVV3=THETA(4)*(WT/70)
V3=TVV3*EXP(ETA(4))
TVKA=THETA(5)
KA=TVKA*EXP(ETA(5))
TVF=THETA(6)
F1=TVF*EXP(ETA(6))
S2=V2

$ERROR
Y = F + F*ERR(1)
IPRE=F

$THETA
  (0,2)          ;[CL]
  (0,50)         ;[V2]
  (0,4)          ;[Q]
  (0,7)          ;[V3]
  (0,1)          ;[KA]
  (0,0.5)        ;[F]
   0.5           ;[WT-CL]
  (0,0.5)        ;[YNG-CL]
```

```
$OMEGA
  0.04          ;[P] omega(1,1)
  0.04          ;[P] omega(2,2)
  0.04          ;[P] omega(3,3)
  0.04          ;[P] omega(3,3)
  0.5           ;[P] omega(4,4)
  0.04          ;[P] omega(5,5)
$SIGMA
  0.09          ;[P] sigma(1,1)

$EST METHOD=1 INTERACTION PRINT=5 MAX=9999 SIG=3 MSFO=083.MSF
$COV

$TABLE ID SID NTIM TAD TIME DV AMT RATE MDV EVID ADDL SS II CMT
ROUTE CTR YNG AGE WT SEX RACE ETHN ETOH SMOK SCR CRCL BUN BSR
ALB AST ALT HCT CWRES PRED IPRE CL V2 V3 Q KA F1 ETA1 ETA2 ETA3
ETA4 ETA5 ETA6 ONEHEADER NOPRINT FILE=083.tab

$TABLE ID TIME CL V2 V3 Q KA F1 ONEHEADER NOPRINT FILE=PATAB083
$TABLE ID ONEHEADER NOPRINT FILE=COTAB083
$TABLE ID ONEHEADER NOPRINT FILE=CATAB083
$TABLE ID IPRE ONEHEADER NOPRINT FILE=SDTAB083
$TABLE ID CL V2 V3 Q KA F1 FIRSTONLY NOAPPEND NOPRINT FILE=083.par
$TABLE ETA1 ETA2 ETA3 ETA4 ETA5 ETA6 ONEHEADER NOPRINT
FILE=083.eta
```