PHARMACOMETRIC ANALYSES OF ANTI-EPILEPTIC DRUGS IN ELDERLY PATIENTS: APPLICATIONS TO CARBAMAZEPINE, GABAPENTIN, AND TOPIRAMATE

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Dedication

To The Memory of My Father

"You left this world to live within me"

To My Wonderful Mother

Abstract

Studies of the pharmacokinetics (PK) and cognitive effects of antiepileptic drugs (AEDs) in the elderly populations remain limited. Optimal dosing of these drugs in the elderly patients requires the characterization of both inter and intraindividual variability in drug disposition and cognitive responses to AEDs. The aims of the current dissertation were to characterize the PK of carbamazepine (CBZ) and gabapentin (GBP), AEDs that are widely prescribed in the elderly population, in community-dwelling and nursing home older patients, respectively, and to conduct a quantitative assessment of covariates that influence the PK parameters of these drugs. We further quantified the effect of TPM, an AED with a unique cognitive signature affecting language use in a subset of patients, on adverse cognitive effects in healthy volunteers. The long-term goal of the latter study is to set the foundation for understanding the drug-induced cognitive impairment in the elderly populations.

The concentration-time and exposure-response data were analyzed by means of nonlinear mixed effects modeling in the NONMEM® software. The population PK model of total and unbound CBZ in community-dwelling elderly patient with epilepsy found age to have no effect on the clearance (CL), volume of distribution or protein binding of CBZ. This model estimated a significant effect of race on the clearance of CBZ, where Caucasians had an average of 30% higher CL than African Americans. On the other hand, the PK characteristics of GBP in a frailer population of nursing home elderly patients were different from both community-dwelling patients and younger adults. We found the CL of GBP in a nursing home resident with a normal renal function (5.78 L/hr) to be slightly less than that of a community-dwelling elderly patient (8.5 L/hr) of comparable renal function. Furthermore, a dose-dependent bioavailability of GBP in nursing home older residents was demonstrated, and the extent of absorption was half saturated at a much lower dose (~480 mg) than in younger adults (~1100 mg). Model-based simulations suggested a substantial increase in systemic exposure with administration of high total daily dose (≥600 mg) as smaller doses of GBP given more often due to the increase in oral bioavailability.

Population pharmacokinetic-pharmacodynamic (PK-PD) models were developed and quantified the effect of TPM exposure on the word-level verbal fluency performance in healthy volunteers. Studies in healthy volunteers enabled us to characterize the effect of TPM on generative fluency as measured by the controlled oral word association (COWA) test while excluding other confounders. We found the performance on COWA to decline in an exponential manner with increased TPM concentration, and that the ratio of COWA scores to baseline decreased by a factor of 0.85, on average, with each mg/L increase in TPM concentration. In addition, the PK-PD model enabled us to quantify and account for the significant practice effect (estimated to be 12% improvement in the COWA scores after the 3rd time the test was administered on drug-free sessions) in modeling the exposure-response profile. The estimated effect of TPM in our study was based on a narrow range of observed concentrations (0.05 – 3 mg/L) and low single oral and intravenous infusion dose (100 mg). As a result, we recommended future studies to administer a wider range of TPM doses to enable the characterization of the dose-response relationship. In conclusions, the results from the PK studies presented in this dissertation found that the elderly population is a heterogeneous group with respect to the PK of AEDs. Thus, extrapolation of results between different age groups within the elderly population may not be valid. Furthermore, the PK-PD analyses of cognitive effects of TPM in healthy volunteers successfully established quantitative models to predict cognitive performance at a particular level of TPM exposure and will be beneficial in generating hypotheses, research design and interpretation of PK-PD findings from future studies in the elderly population.

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Chapter I

Introduction

1.1 EPILEPSY

Epilepsy is a chronic neurological disorder that affects more than 3 million persons in North America.[1] The overall incidence of epilepsy is reported to be 100,000 cases per year across the United States.[2] Both the occurrence of at least one epileptic seizure and persistent alterations in the brain functions that increase the likelihood of future seizures are required for defining epilepsy. Epileptic seizure is a symptom of an underlying disorder (genetic, traumatic, metabolic, malignant, etc) which causes abnormal excessive and disorderly neuronal activity.[3] Diagnosis of seizures is usually based on patient's history, physical examination, electroencephalographic studies, laboratory tests and neuroimaging, and aims at identifying both the existence and the type of seizure.[2] Often clinicians ask the patient or a close family member about a family history of epilepsy, birth complications, history of infection or head trauma and alcohol or drug abuse.

Physical examination and laboratory tests may confirm any of such causes of seizures, however, in ~70% of the cases, seizures are of cryptogenic or idiopathic origins for which no identifiable insult is determined.[1] EEG can confirm the presence of abnormal electrical discharges, the type of seizure and the location of the brain focus.[4] Multiple EEGs may be required when no abnormalities are shown on the first EEG, since approximately 50% of patients with epilepsy show no abnormalities on the first EEG. Magnetic resonance imaging (MRI) can also be used to reveal small lesions due to tumors which may not be evident on computed tomography (CT).[2]

An incorrect diagnosis can have serious consequences for the patient, including potential exposure to toxic medications, loss of driving privileges and social stigma.[1] Furthermore, establishing the type of seizure is important in developing the patient's treatment plan. According to the International League Against Epilepsy, epileptic seizures are classified as partial, generalized, unclassified or status epilepticus.[5] Partial seizure onsets in a specific part of the brain and can be simple, complex or can secondarily generalize to other brain areas. Generalized seizures commonly include absence and primary generalized tonic-clonic seizures.[6] Examples of anti-epileptic drugs (AEDs) that are approved for a particular seizure type are carbamazepine, oxacarbazepine, and phenytoin

for partial seizures, and ethosuximide and divalproex sodium for absence (petit mal) seizures.[7] Approximately, 70% of patients are responsive to one or a combination of these drugs, while refractory cases (20-40% of patients) may need alternative therapies such as vagus nerve stimulation or brain surgery.[8]

1.2 EPILEPSY IN THE ELDERLY

Both the prevalence and the incidence of epilepsy are dramatically higher among elderly persons than younger adults.[9] The best estimate of the incidence of epilepsy in the United States comes from a Hauser et. al. study in Rotchester, Minnesota. During the decade of 1975-1984, the average incidence of epilepsy was 31 per 100,000 people-year in young adults compared to an average of 156 per 100,000 people-year in the elderly population.[9] Even more, estimates of incidence and prevalence show marked heterogeneity within the elderly population and are thought to be based on age, clinical setting and the degree of frailty of the old person.[10,11] During the years of 1997-1999, the prevalence of epilepsy in a community-dwelling elderly sample of 1,130,155 veterans 65 years old was 1.8%.[12,13] After admission to the nursing home, the incidence of epilepsy was roughly estimated to be 600 per 100,000 persons-3 months; an estimate that is 3 times larger than that in the community-dwelling elderly.[14] In addition, it is estimated that approximately 10% of all nursing home residents are prescribed at least one AED with 6% being taken for epilepsy or seizure indications.[15-17]

Further heterogeneity is observed within the particular elderly groups and could be attributed to the complexity of the medical conditions or the frailty of the person. Leppik, I. E., recommended subgrouping the elderly into healthy patients, subjects with multiple medical problems and frail elderly.[11] Surprisingly, AED use amongst these groups was found to be inversely related to age, despite the fact that both the prevalence and incidence of epilepsy increase with advancing age.[11,18] Possible reasons for this paradoxical pattern could be related to the different causes of epilepsy amongst the age groups and the severity of the disorder in young-old subjects. Many seizures in the oldest-old subjects are not epileptic.[19] A convulsive syncope in the elderly can be due to a cardiovascular problem, electrolyte or metabolic imbalance, or even a febrile illness. This

can easily be misdiagnosed as epilepsy and would be differentiated through electrocardiograms and clinical laboratory testing coupled with an EEG study.[11]

1.3 PHARMACOTHERAPY OF EPILEPSY

Before the initiation of therapy, key decisions are to be made about when to start treatment, which AED to select and how to individualize treatment so that a maximum benefit-to-risk ratio of a particular option is attained. While the selection of a first-line AED is mainly based on effectiveness against a particular type of seizure, patient-specific factors such as age, comorbidities, childbearing potential and concomitant medications need to be considered. Currently, there are more than 20 AEDs that are available for the treatment of epilepsy. An examination of the FDA-approved indications for AEDs shows that there are more AEDs approved for partial than generalized or other types of seizures and that almost all new AEDs were initially approved for use as adjunctive (add-on) therapies to the existing AEDs. In addition to its use in epilepsy, AEDs are increasingly used in the treatment of nonepileptic neurological and psychiatric conditions.[20] These include trigeminal neuralgia, neuropathic pain and bipolar disorder. Table 1.1 lists the FDA approved indications of AEDs in both epilepsy and other conditions.

1.4 CLINICAL STUDIES IN SPECIFIC POPULATIONS: A DRUG DEVELOPMENT PERSPECTIVE

1.4.1 Studies in Healthy Volunteers

A healthy volunteer is defined by the Royal College of Physicians to be an "individual who is not known to suffer of any significant illness relevant to the proposed study, who should be within the ordinary range of body measurements, such as weight, and whose mental state is such that he is able to understand and give valid consent to the study".[45,46] Recruitment of healthy volunteers poses several challenges, and there is a high variability among clinical studies in defining the meaning of being healthy.[45] Furthermore, it is sometimes difficult to justify testing drugs with a high toxicity profile in healthy volunteers, because the risk would supersede the benefits of the drug in healthy subjects. Phase 0 studies allow testing of high risk drugs in healthy volunteers by administering

subtherapeutic micro-doses in a small number of subjects.[47] Such trials are not designed to substitute for phase I dose-escalation and safety studies. It is usually conducted for certain purposes in early clinical development such as assessing the bioavailability of less tolerable drugs (e.g. antipsychotics and antiepileptics) in humans and supporting smaller phase I and II trials by excluding drugs of unfavorable PK characteristics.[48] Studies in healthy volunteers can additionally be useful in investigating the mechanism of drug action or adverse effects without interference from the underlying pathological condition. In the latter instance, one can assume a situation where assessing the adverse cognitive effect of a new AED in patients with epilepsy would be difficult since those patients are, by the nature of their disorder, more prone to cognitive deficits. In this case, studies in healthy volunteers would be helpful in estimating the effect of the test drug on cognition while excluding other factors related to the etiology of epilepsy or other conditions. In a contradictory situation, measures of cognitive enhancement of a new CNS-acting drug in healthy volunteers can serve as a proof-of-concept in selecting an efficacious dose to be tested in a phase II clinical study (for instance, in patients with Alzheimer disease).

1.4.2 Studies in the Elderly Subjects

Elderly subjects, especially those who are older than 75 years, are among the populations that are underrepresented in clinical studies. The reasons behind exclusion of this population could either be related to the elderly patients themselves or the research design.[51-53] One study found elderly who were receiving fewer medicines to be less likely to give consents for study participation.[52] Another review of 251 registered clinical trials on heart failure, a leading cause of hospital admissions in older persons, identified study design issues and unjustified exclusion criteria (upper age limit, comorbidity, cognitive impairment, polypharmacy) as the main contributors to the widespread exclusion of elderly patients in these studies.[52] There have been increasing calls for appropriate representation of the elderly in large-scale clinical trials. McMurdo et al, argues that the established benefits in young adults cannot be extrapolated to the frail elderly population and suggests that ethics committees demand proper justifications for age restrictions in study protocols, and the regulatory agencies to approve the use of new drugs in the population who participated in its evaluation.[54] Exclusion of older people from clinical

studies creates difficulties for both clinicians and disadvantaged elderly patients. A 2004 multicenter Veteran Affairs study found that 92% of frail elderly patients received inappropriate medications. Of these, 50.9% received an inappropriate dose, and 47.1% had an inappropriate duration of therapy. Other problems include failure to consider drug-drug interactions (6.3%) and drug-disease interactions (20.4%).[55] Interestingly, the latter study identified an association between factors as polypharmacy and health status, often are the basis for unjustified exclusions of elderly from clinical trials, and the prevalence of inappropriate drug use.[55] The PREDICT (increasing the Participation of the Elderly In Clinical Trials) consortium has asked for specific regulations, similar to those concerning drugs developed for use in children, to be released by regulatory agencies to create a positive approach for inclusion of older subjects. This approach is anticipated to only impact the conduct of clinical studies designed for registration purposes. A comprehensive approach to tackle this problem should involve ethics committees, institutional review boards, researchers and drug regulators, consider the inclusion of members with geriatric expertise on ethics, research and regulatory teams and ensure that proper justifications for exclusion criteria are provided in the study protocols.[56]

1.5 POPULATION PHARMACOKINETIC/PHARMACODYNAMIC MODELING

1.5.1 Population Pharmacokinetic Modeling

Population pharmacokinetics (PPK) provides a quantitative tool to evaluate the sources of intersubject variability and the relative importance of each in influencing the dose-concentration relationship. PPK analysis is particularly useful in handling sparse heterogeneous data collected during both prospective and observational studies. PPK models usually identify two levels of hierarchy: at the first level, the individual observations are assumed to arise from a probability model $f(C|\theta)$ for which the mean is given by the structural PK parameters (θ) and the variance is modeled to represent measurement errors, model misspecifications and other sources of uncertainty in the individual concentrations. This can be written as:

$$C_{ij} = f_{ij}(\theta_i, t_{ij}) + \varepsilon_{ij} \qquad \text{equation (1)}$$

where C_{ij} is the observed concentration of the ith individual at the jth time (t_{ij}), f_{ij} denotes the PK function for predicting the jth concentration in the ith subject and ε_{ij} is the jth residual error in the ith subject. At the second level, random effects are modeled and give rise to individual realizations of the PK parameters. The variance of the random effects provides a quantification of the intersubject variability in the PK parameters and can be explained by subject-specific covariates.

$$\theta_i = g(\theta, x_i) + \eta_i \qquad \text{equation (2)}$$

Where g is a function that models the expected value of θ_i given the known predictor variables x_i, population parameters, and a realization η_i from the random distribution of ETA.[57] Nonlinear mixed effects modeling is a common statistical method used to obtain the estimates for both the PK and variability parameters. Amongst the variety of estimation methods, the maximum likelihood approach is widely used in estimating the parameters of the population model. This approach obtains a set of parameters $\hat{\theta}$ that globally maximizes the log likelihood function or minimizes the -2 of the log likelihood, at least to a proportionality constant, (-2LL; NONMEM 7). In NONMEM, the maximized likelihood is an extended least square (ELS) function. The ELS does not lend itself to a straightforward maximization since the model is nonlinear in both η and ε. Therefore, various linearization methods were introduced to approximate the integral of the marginal likelihood $L_i(\theta, \Omega | C_i)$. The first order (FO) approximation expands the model about the random variables η and ε, and evaluates the expression at their expected value of zero. The first order conditional estimation (FOCE) method utilizes a more advanced expansion method by evaluating the expression at the individual's post-hoc conditional estimate of η and the expected value of the mean ε_i (zero), and does not include an $\eta - \varepsilon$ interaction term unless specified. The Laplacian integral approximation introduces an additional second order term which is also evaluated at the empirical bayes estimate of η.[58-60] The PPK approach plays a pivotal role in model-based drug development.

PPK is able to leverage both efficacy and toxicity data collected in early phases of clinical development (phase I and IIb) to provide more informative designs for late-phase development trials and analyses. It can also be used to evaluate pharmacokinetics and response data in special populations during phase III and IV studies; thus providing a rational design of dosing regimens in this patient population.

1.5.2 Exposure-response Modeling

Exposure-response modeling (often called PK-PD) refers to the development of quantitative models to establish the relationship between the efficacy and toxicity induced due to a particular exposure (dose, concentration, AUC, etc) from the drug. During early phases of clinical development, PK-PD modeling and simulations can provide substantial support to translate the findings from preclinical stages into a safer, mechanism-based selection of first-in-human doses in phase 1 studies. These models can further be utilized in supporting the proof-of-concept studies by confirming that the hypothesized mechanism is influenced by the investigational drug. Later in clinical development, PK-PD models can be used to simulate the probability of success of competing doses for large-scale phase III studies, evaluate the clinical significance of drug-drug or drug-disease interactions, guide the use in the target populations and optimize the dose and dosing regimens in particular subpopulations.[61,62]

1.5.3 Exposure-response Modeling of Count Outcomes

A count random variable defines the number of discrete occurrences of events that take place during a given time interval. Count outcomes are often encountered in development programs or studies that aim at identifying the effect of a pharmacological agent on the occurrence of unfavorable events; for instance, seizure counts and number of adverse drug reactions.[63] The utility of PK-PD models in establishing the exposure-response relationship for a count outcome measure goes beyond understanding the relationship between concentration and response. It is found to be advantageous in exploring the time course of the disease or the event of interest, the heterogeneity in response as explained by the presence of a mixture of populations, and the contribution of explanatory covariates in modifying the exposure-response relationship.[64]

Various models have been developed to model the exact nature of count outcomes, of which the Poisson (PS) distribution is the most commonly used. The PS function defines the probability of occurrence of an exact number of events at a specified period of time under the assumption that the occurrences are independent of one another:

$$f(n;\mu) = \frac{e^{-\mu} \times \mu^{n}}{n!} \qquad \text{for n} = 0, 1, 2, ... \qquad \text{equation (3)}$$

Where n is a non-negative integer, and μ is a positive real number that represents the expected number of events during a given time interval. An important property of the PS distribution is that the mean number of events is equal to the variance: $E(f) = \text{var}(f) = \mu$. In addition, when μ is large (approximately >10), the PS distribution can be approximated by the normal distribution: $Poi(\mu) \approx N(\mu, \mu)$. The log link is considered to be the canonical link function for modeling the mean of a PS-distributed random variable. In PK-PD modeling, the mean μ is linked to exposure, time of progression and individual's specific covariates.

Count outcomes collected in the clinical settings often violate the assumptions of the PS distribution. These data are heterogeneous in nature, display high variability and are usually collected from a mixture of populations at different clinical settings. In this case, the variance is expected to be greater than the mean; a common phenomenon known as overdispersion (OVDP). Alternative modeling approaches in such cases are available through other distribution functions (e.g. negative binomial, NB), mixture modeling or inclusion of explanatory covariates to account for the observed heterogeneity of the data. In addition, the memoryless assumption of the PS is often violated by PD outcomes that show interdependency between neighboring observations. In patients with refractory epilepsy treated with pregabalin as an add-on treatment, for instance, a strong association was found between the counts of seizures occurring on a particular day and that on the previous day. Patients with zero counts on the previous day were more likely to have zero seizures on the next day and vice versa.[63] This feature is accounted for by considering a markovian element that models the interdependence of consecutive measurements. Other characteristics of the clinical count outcomes are the presence of repetitive time intervals

with no observed events (zero inflation) and the existence of a combination of both zero inflation and OVDP in the data. In the latter cases, the implementation of zero-inflated PS and zero-inflated NB distributions, respectively, can provide useful modeling alternatives.[65]

1.6 SCOPE OF THE DISSERTATION WORK: PHARMACOKINETICS AND COGNITIVE RESPONSES OF ANTIEPILEPTIC DRUGS IN SPECIAL POPULATIONS

The overall aim of this dissertation work was to characterize the effect of aging on the pharmacokinetics and cognitive response of AEDs in special populations of elderly patients (community-dwelling and nursing home residents). Population PK studies focused on understanding the effect of advanced age on absorption, distribution, metabolism and elimination of AEDs. As the data on the mechanism and PK/PD profile of drug-induced cognitive impairment are still limited, we sought to characterize the variability in exposure-response of cognitive function in adult healthy volunteers. Our long-term objective is to use these studies as a basis for understanding the cognitive effects of AEDs in the elderly patients.

1.6.1 Pharmacokinetics of Unbound and Total Drug Concentrations Following Intravenously Administered Carbamazepine in Elderly and Younger Adult Patients with Epilepsy

Carbamazepine is widely used in the treatment of partial seizures, generalized tonic-clonic seizures and trigeminal neuralgia.[66] Clinical PK of CBZ has been extensively studied over the years. CBZ is completely absorbed from the gastrointestinal tract (bioavailability 85 to 100%), however, absorption is reported to be slow and irregular. It is extensively metabolized in the liver, mainly by CYP3A4/5 isoenzymes with ~98% of the dose excreted in the urine as metabolites.[67] CBZ-10, 11-epoxide, a primary metabolite of CBZ, has shown a comparable efficacy to the parent compound.[68] Due to the auto-induction of its metabolism, the half life of CBZ is reported to be lower after repeated administration (10 to 20 hours) than single doses (18 to 65 hours).[67] CBZ is a lipophilic drug that is widely distributed through the body. It is 70-80% bound to plasma protein,

mainly to albumin and alpha 1-acid glycoprotein (AAG). A majority of PK studies of CBZ involve children and young-adults with very few reports investigating the effect of advancing age on CBZ PK. With the complex PK, high potential for drug-drug interaction, narrow therapeutic window (unbound CBZ 0.87 – 2.8 mg/l), and large interindividual variability in PK, prescribing CBZ in the elderly based on dosing recommendations from young adults would not be adequate. Systematic PK studies are thus needed for evaluating the influence of ageing on the PK and activity of cytochrome P450 enzymes in the metabolic pathway of CBZ. **Chapter Two** of this dissertation reports the population PK of CBZ in community-dwelling elderly and younger adults following a novel intravenous (IV) stable-labeled formulation administered in patients with epilepsy. The use of an IV SL formulation of CBZ enabled study of the effect of old age on CBZ clearance while excluding variability due to absorption/bioavailability. We analyzed both total and unbound CBZ concentrations, estimated the free fraction of CBZ in the plasma and investigated the possibility of nonlinear plasma protein binding in this population. In addition, we considered the potential influence of other factors such as sex, race, body size measurements and albumin concentration on the PK of CBZ in this patient population.

1.6.2 Examination of Gabapentin Pharmacokinetics and Optimal Dosing in Elderly Nursing Home Patients

Gabapentin is approved by the United States FDA for the adjunctive treatment of partial seizures in adults and children, and is recommended as a first-line treatment of neuropathic pain in the elderly patients.[39] GBP is neither metabolized in the body nor does it bind to plasma proteins. It is excreted unchanged in the urine, and the cumulative amount excreted relative to the administered dose of GBP is often used as a measure of bioavailability. Renal impairment is therefore reported to decrease GBP elimination and to necessitate a dose reduction.[69] Unlike CBZ, GBP bears no clinically significant drug-drug interactions with other anticonvulsants.[70] Absorption of GBP however exhibits a nonlinear saturable behavior, with increased doses resulting in a less-than-proportional increase in plasma concentration. GBP is mainly transported through the gut via an L-amino acid transport system that becomes saturated at the range of clinically utilized

doses.[71-73] In addition to the lack of drug interactions, GBP is an ideal drug to be used in the elderly owing to its favorable tolerability profile in this population.[74] A previous PK study of GBP in community-dwelling elderly patients found creatinine clearance (CrCL) and race to be the only determinants of GBP clearance (CL) in this patient population. Advancing age had no effect on the GBP CL after accounting for CrCL, and the study concluded that dosage adjustment in the elderly should only be done on the basis of renal function.[75] Whether these results can be extrapolated to the institutionalized elderly patients is unknown. The latter population may differ from community-dwelling old persons in many ways: nursing home elderly are thought to be frailer, more dependent and cognitively impaired than community-dwelling elderly. A recent meta-analysis of 77 follow-up studies that evaluated predictors of nursing home admissions in the US found older age, three or more dependencies in performing once of activities of daily living, Caucasian race, and indicators of functional and cognitive impairment to be strong predictors of nursing home admissions.[76] Nursing home residents are also reported to suffer numerous comorbidities and receive more medications than noninstitutionalized patients.[78] In addition, the inappropriate use of drugs was identified as a significant risk for transition to nursing home amongst community-dwelling elderly.[77] The nursing home population may therefore have distinct PK and PD characteristics from community-dwelling elderly, and PK/PD studies in this population are needed before appropriate dosing guidelines can be created for the elderly nursing home residents. **Chapter three** of this dissertation reports the findings from our prospective PK study of GBP in nursing home elderly patients with chronic pain. We investigated the influence of aging on the nonlinear saturable absorption characteristics of GBP in this patient population. Furthermore, the relationship between kidney functioning and GBP CL was established, and the results were contrasted with community-dwelling elderly and healthy younger adults. Finally, a model-based simulation study of the effect of saturable absorption and dosing schedule on steady state concentration of GBP in the nursing home elderly was conducted.

1.6.3 Pharmacokinetic/Pharmacodynamic Modeling of Topiramate-induced Cognitive Impairment

Topiramate is indicated as a monotherapy for newly diagnosed partial epilepsy, an add-on treatment for resistant partial-onset seizures and a prophylactic treatment for migraine. It is also being prescribed for a range of other conditions including obesity, pain, bipolar disorder, and alcoholism.[79] The broad spectrum activity of TPM is attributed to its multiple PD targets in the synapse.[80] On the other hand, some of these effects, especially the inhibitory effect on the AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) and kainite subtypes of glutamate receptors, are thought to be mediating TPM-induced cognitive impairment.[79] TPM is an ideal drug for studying the mechanism and variability in cognitive responses, especially language-related difficulties, to AEDs. TPM has a selective and unique signature on verbal fluency and working memory in only a subset of patients who develop severe effects causing discontinuation of therapy. [81,82] Moreover, the frequency of cognitive complaints across studies of patients using TPM varies from as low as 1-5% to up to 44%.[83,84] Factors such as the effect of polytherapy, titration schedule, maintenance dose and the underlying etiology of epilepsy has partially accounted for the interindividual variability in the cognitive response to TPM; however, the relationship to drug exposure has not been thoroughly evaluated.[85,86] Cirulli et al, previously found TPM plasma concentration to have the largest influence on changing of verbal fluency scores and working memory tests on a battery of 11 cognitive tests given to healthy volunteers after a single TPM dose of 100 mg (r^2 ranged from 0.07 to 0.23).[87] In addition, Marino et al, reported a strong association between TPM blood levels collected after a single dose of 100 mg in healthy volunteers (n=20) and measures of spontaneous speech and verbal recall.[88] A population PK/PD model of the exposure-response profile as it relates to cognitive responses provides a statistically powerful and clinically useful approach to understanding TPM-induced cognitive impairment. This approach offers a quantitative assessment of both the relationship between TPM exposure and cognitive responses and the magnitude of interindividual variability in the parameters of the exposure-response relationship. Furthermore, it allows the rigorous evaluation of explanatory environmental and demographic factors which may contribute to the variability in response, and is the basis for predicting the drug-induced cognitive

impairment at higher exposure or chronic dosing of TPM. **Chapter four** of this dissertation tackles the latter issues through the development of a PK/PD modeling approach to characterize the effect of acute low doses of TPM on phonemic generative fluency in adult healthy volunteers. Recruiting healthy volunteers enabled studying of the mechanistic aspects of TPM's effects on cognitive function, while excluding other confounding variables such as polytherapy, epilepsy, and other neurological conditions. In addition, we conducted a comprehensive evaluation of the subjects' characteristics for their influence on the parameters of the exposure-response relationship. Results from this study have also provided the guidance for designing future trials that will aim at characterizing the mechanistic aspects of cognitive performance at much wider range of exposure and target population than were considered in the current study.

Table 1.1. US FDA Approved Indications for AEDs.

AED	Seizure type	Age (yrs)	Other indications	Monotherapy	Approved on
Carbamazepine	CP; GTC; Mixed	NA	Trigeminal & Glossopharyngeal neuralgia	NA	03/11/1968
Clonazepam	LGS; Akinetic; Myoclonic; Absence	NA	Panic disorder	Yes	06/04/1975
Clorazepate	Partial	NA	Anxiety disorders; Withdrawal symptoms of alcoholism	No	06/23/1972
Diazepam	Convulsive disorder; Status epilepticus	NA	Anxiety disorder; Acute alcohol withdrawal; Skeletal muscle spasm	No	11/15/1963
Ethosuximide	Absence	NA	--	NA	11/02/1960
Phenobarbital	GTC; Cortical local; Status epilepticus	--	Insomnia; Preanesthetic; Sedative	--	--
Phenytoin	GTC; Psychomotor; CP; Seizures following neurosurgery	NA	--	NA	01/06/1953
Pregabalin	Partial seizures	Adult	Neuropathic pain; Postherpetic neuralgia	No	12/30/2004
Primidone	Grandmal; Psychomotor; Focal	--	--	Yes	03/08/1954
Valproic acid	Simple; Complex absence; Multiple types	NA	--	Yes No	02/28/1978
Felbamate	Partial with and without generalization; Partial and generalized in LGS	Adults Children	--	Yes No	07/29/1993
Gabapentin	Partial with or without secondary generalization	>3	Postherpetic neuralgia	No	12/30/1993
Lamotrigine	Partial; Generalized in LGS	>1	Bipolar disorder	Yes (>16 yrs)	12/27/1994

AED	Seizure type	Age (yrs)	Other indications	Monotherapy	Approved on
Lacosamide	Partial	>16	--	No	11/29/2007
Levetiracetam	Partial; Myoclonic	>4	--	No	11/30/1999
Oxcarbazepine	Partial	>2	--	Yes (> 4 yrs)	01/14/2000
Rufinamide	LGS	>3	--	No	14/11/2008
Tiagabine	Partial	>12	--	No	09/30/1997
Topiramate	Partial; Primary GTC; LGS	>2	Prophylaxis of migraine	Yes (> 10 yrs)	12/24/1996
Zonisamide	Partial	Adults	--	No	03/27/2000
Vigabatrin	Infantile spasms; Refractory CP	Children Adults	--	Yes No	08/21/2009

AED: Antiepileptic drug; GTC: Generalized tonic-clonic; LGS: Lennox-Gastaut syndrome; NA: Not available

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Chapter II

Population Pharmacokinetics of Unbound and Total Drug Concentrations Following Intravenously Administered Carbamazepine in Elderly and Younger Adult Patients with Epilepsy

2.1 INTRODUCTION

Epilepsy is a common neurologic disorder defined by a history of at least one seizure together with a diagnosed alteration in the brain that increases the likelihood of future seizures.[1] It affects about 50 million people worldwide including approximately 3 million residents of North America.[2] Carbamazepine (CBZ) is a standard treatment for partial seizures as well as trigeminal neuralgia and psychiatric disorders.[3] In comparative trials with other antiepileptics, CBZ showed similar results to lamotrigine [time to 12-month remission (HR) 0.91(95% C.I. 0.77-1.09)][4,5] but superior efficacy to phenobarbital and primidone for the treatment of partial seizures.[6] However, 30-40% of patients with epilepsy respond poorly to CBZ or develop adverse effects which could be attributed to the complex pharmacokinetics of CBZ and the limited knowledge of individual factors influencing its disposition.[7]

CBZ is extensively metabolized by the liver, in part through the cytochrome P450 enzyme system (CYP3A4/5). Several factors may influence serum concentrations of CBZ and its metabolites. In the elderly (age $\geq$ 65-70), the population clearance of CBZ is reported to decrease by 25-40%[8] and is likely to be due to a decreased activity of CYP3A4.[9] Co-prescribed drugs such as phenytoin and phenobarbital are reported to increase CBZ clearance in both adults and children due to induction of the metabolizing enzymes.[10,11] In addition, the unbound fraction of CBZ might be affected by changing levels of the major binding proteins, albumin and alpha 1-acid glycoprotein (AAG).[12]

The variability in CBZ pharmacokinetics (PK) is presumably due to the complex PK and the narrow therapeutic window of the drug (unbound CBZ 0.87 – 2.80 mg/l).[13] Elevated serum CBZ concentrations are associated with neurologic side effects, and hyponatraemia.[14] Similarly, clinical effects of CBZ bear a relatively close relationship to serum drug concentration.[15] CBZ PK following oral administration have been extensively studied,[8,10,13-18] but there are a few reports involving the PK of IV CBZ in either healthy volunteers or epilepsy patients.[19-22] The safety of an IV CBZ formulation in patients has previously been assessed.[23] In the current study we investigated the population PK of total and unbound CBZ from a novel stable-labeled (SL) IV formulation. This allowed us

to examine CBZ disposition in community-dwelling elderly and younger adult patients with epilepsy without interrupting therapy.

2.2 METHODS

2.2.1 Patient Selection and Recruitment

Patients were recruited from three epilepsy programs: the University of Minnesota and affiliated clinics, the University of Miami, and Emory University. Inclusion criteria included requirements that subjects be on CBZ monotherapy or taking non-interacting medications and were over the age of 18. In addition, patients had to be on a stable maintenance CBZ regimen with no dosage adjustments within two weeks prior to the first day of the study. Exclusion criteria included patients with serious medical problems that could compromise their tolerance to IV CBZ or influence the drug disposition. The University of Minnesota Institutional Review Boards (IRB), Miami Veteran Affairs Medical Center IRB, and Emory University IRB approved the study protocol and all patients provided informed, written consents prior to enrollment.

2.2.2 Study Design

Upon admission to the research center, detailed medication history was collected and a brief neurological examination was performed on every patient by the clinical site neurologists. Prior to drug administration, a normal saline infusion was started at 50 mL/hr and continued until 30 minutes after the infusion. Patients were maintained on a steady-state oral CBZ therapy. On the day of the study, subjects received a total of 100 mg SL CBZ (10 mg/mL in 22.5% 2-hydroxypropyl-β-cyclodextrin) as an infusion over a period of 10-20 minutes. The SL isotope methodology allowed the IV CBZ to be analytically differentiated from the oral CBZ due to the different masses of CBZ in each formulation. Blood sampling was done at 0, 0.083, 0.25, 0.5, 1, 2, 4, 6, 10, 24, 48, 72, and 96 hours. At the end of the infusion, subjects were allowed to take their regular morning CBZ dose less 100 mg. Blood samples were centrifuged and the plasma was frozen at -20 ^{o}C until assayed.

2.2.3 Intravenous Formulation

A general description of the synthesis and formulation of the SL-CBZ is reported in a previous publication.[23]

2.2.4 Carbamazepine Assay

Plasma concentrations of unbound and bound SL-CBZ were analyzed by a validated liquid-chromatography/mass spectroscopy. Carbamazepine-d_{10} (CBZ-d_{10}, C/D/N Isotopes, Quebec, Canada) was used as the internal standard. 0.5 mL of patient plasma and 20 μL of internal standard were mixed with blank plasma and extracted with 3 volumes of ethyl acetate. Following each centrifugation, the organic layer was removed and evaporated under nitrogen to dryness. Each sample was then redissolved in 25 μL of ethyl acetate. Unbound drug was separated from the bound fraction by using Millipore-Amicon Centrifree filters. The mobile phase consisted of 50% 0.05 M ammonium acetate buffer (pH 4.7) and 50% methanol and was run at a flow rate of 0.4 mL/min on a Zobrax LC8 (3.0x150 mm, 3.5μ) column. All samples from an individual patient were run at the same time along with a 7-concentration standard curve and low, medium and high concentrations of quality control samples (range: 0.1-4 μg/mL). The lower limit of detection was 0.1 μg/mL for SL-CBZ. The assay was validated by being repeated five times on several days. The between-day and within day variability of the assay was 3.5% and 2.5%, respectively. Accuracy ranged between 83.7 and 102.6% for the analytical standard. Quality control samples were all within $\leq$ 10% with respect to variability.[21]

2.2.5 Population Pharmacokinetic Analysis

The population PK analyses were performed using the nonlinear mixed effects modeling approach as implemented in NONMEM (version VII, level 1.2). The first-order conditional estimation with interaction (FOCEI) was utilized throughout the model development process. Based on exploratory data analysis, the basic pharmacokinetic model was selected and fit to the data. A one-compartment (ADVAN1) and two-compartment model (ADVAN3) with first-order elimination were explored. The kinetics were parameterized in terms of the unbound parameters including clearance (CL),

volume of distribution (V_1), unbound fraction (F_u), and for the two compartment model intercompartmental clearance (Q), and peripheral volume (V_2). In this analysis, the total concentration was assumed to be a function of the unbound concentration as follows:

$$C_{Tpred,ij} = \frac{C_{Upred,ij}}{F_{u,i}}$$

Where $C_{Tpred,ij}$ and $C_{Upred,ij}$ are the j[th] predicted total and unbound plasma concentration (mg/L), respectively, in the i[th] individual, $F_{u,i}$ is the unbound fraction for the i[th] individual. This model assumes a constant F_u for an individual but can be modified to allow concentration or time dependencies. The effect of unbound drug concentration (C_u) on F_u was modeled through a linear slope function as follows:

$$F_{u,ij} = F_{u,i,Base} + S \times C_{Upred,ij}$$

Where $F_{u,i,Base}$ is an intercept of F_u for the i[th] individual and S is the estimated increase in F_u for a unit mg/L increase in the C_u.

The inter-individual variability in the PK parameters was modeled through an exponential error model as given in equation 1:

$$\beta_i = TV\beta \times \exp(\eta_{i,\beta}) \qquad (1)$$

Where β_i is the individual PK parameter, $TV\beta$ is the population mean PK parameter, and $\eta_{i,\beta}$ is the independent random error distributed normally with a mean zero and variance equal to Ω^2_β, which specifies the between-subject variability around the $TV\beta$.

Different error models were explored including an exponential model, proportional model, additive model, and combined proportional and additive error model. Because unbound and total concentrations were simultaneously modeled, an indicator variable (TYPE) was used to build separate residual error models for unbound and total concentrations as shown in equations 2, and 3, respectively:

$$C_{Uobs,ij} = C_{Upred,ij} \times (1 + \varepsilon_{1,ij}) \text{, if TYPE is unbound} \quad (2)$$

$$C_{Tobs,ij} = C_{Tpred,ij} \times (1 + \varepsilon_{2,ij}) + \varepsilon_{3,ij} \text{, if TYPE is total} \quad (3)$$

Where $C_{Uobs,ij}$ is the jth observed unbound plasma concentration (mg/L) in the ith individual, $C_{Tobs,ij}$ is the jth observed total plasma concentration (mg/L) in the ith individual and ε_{ij} is the independent, normally distributed error, known as the residual error (between the predicted and observed concentration) with mean zero and variance σ_{ε}^{2}. Model development was guided by examining diagnostic plots including plots of observed versus population and individual predicted concentrations and conditional weighted residuals versus predicted concentration and time plots.

2.2.6 Covariate Model

Scientific hypotheses regarding covariate effects on CBZ model parameters were tested. Covariates examined included age, body size measurements (including total body weight (TBW) in kg; body surface area [BSA]; ideal body weight [IBW]; and lean body weight [LBW]); demographic covariates (including race; sex; and clinical center), factors that may affect drug metabolism (smoking status; alcohol consumption; grapefruit juice consumption), and covariates that may influence drug binding (such as AAG, albumin, total protein concentration, and C_u).

Covariate modeling was done using the standard forward inclusion/backward elimination approach and was initially guided by observation of plots of posterior Bayesian estimates of PK parameters versus the different covariates. Continuous covariates, such as age, protein concentrations, and C_u were investigated through linear and non-linear regression on clearance and free fraction. Age was additionally tested as a categorical covariate on both clearance and protein binding (age <60 years, age≥60 years). When evaluating TBW, allometric scaling was used.[24] Categorical covariates were examined according to a multiplicative model in order to obtain the associated fractional change in pharmacokinetic parameters. The covariate model selection was done on the basis of the

change in the NONMEM objective function value (OFV), clinical importance of the estimated effect, as well as visual inspection of diagnostic plots. A decrease in the NONMEM OFV of at least 7.88 (χ^2, $p \leq 0.005$, $df = 1$) and 10.83 (χ^2, $p \leq 0.001$, $df = 1$) was used as a cutoff value for forward inclusion and backward elimination, respectively.

2.2.7 Model Evaluation

The Nonparametric Bootstrap

The precision of the final parameter estimates were checked using 1000 separate NONMEM runs on resampled (with replacement) datasets. The bootstrap analysis was done through the model evaluation option in PDx-Pop 4.1 (ICON Development Solutions, Ellicott City, MD) interface for NONMEM. The results were exported to SAS (version 9.2) and the 2.5^{th} and 97.5^{th} percentiles of the rank ordered parameter values were computed as the lower and upper boundary of the bootstrap 95% confidence interval (CI). Finally, bootstrap parameter estimates as well as their 95% CI were compared to the NONMEM estimates from the original data set.

2.2.8 Model Qualification

The final model was qualified by visual predictive check (VPC) where the estimated parameters were used to simulate 1000 replicates of the original dataset. The 5^{th}, 50^{th}, and 95^{th} quantiles of the simulated CBZ concentrations were plotted against observed concentrations. The simulations were done using the PDx-Pop 4.1 interface for NONMEM.

2.3 RESULTS

2.3.1 Model Building Data Set

The final data set used was comprised of 833 observations of unbound concentrations and 1201 observations of total concentrations from 113 subjects: The University of Minnesota and affiliated clinics [median age 43, range (20-87)], the University of Miami [47 (22-82)], and Emory University [34 (19-61)]. Patients received a total infusion dose of SL-CBZ in the range of 87 mg to 130 mg at an average rate of 9 mg/min. Table 2.1

summarizes patient characteristics at baseline as well as potential covariates used in the analysis.

2.3.2 Population Pharmacokinetic Analysis

2.3.2.1 The Structural Pharmacokinetic Model

A two-compartment model with first order elimination (subroutine ADVAN3, TRANS4) adequately fit the data. Both alpha and beta phases of the two compartment disposition could be supported by the unbound and total SL-CBZ concentration-time profiles shown in Figure 2.1A and 2.1B. The one-compartment model resulted in a poorer fit to the data and a significantly higher OFV. The proportional error model and the combined proportional and additive error model best described the residual unexplained variability in the unbound and total concentrations, respectively.

2.3.2.2 Covariate Model

Final model parameter estimates as well as the precision associated with the estimation are shown in Table 2.2. During the forward selection process, race was found to be the only covariate that had a significant influence on CBZ unbound clearance (ΔOFV = 13.4, $p<0.005$). Caucasians were found to have an average of 30% greater unbound clearance compared to African Americans. Body size measurements, age (tested as a continuous or categorical covariate), smoking category, alcohol use or grape fruit consumption, plasma albumin and AAG concentration had insignificant effects on the unbound clearance either through univariate inclusion or after accounting for the race effect (ΔOFV <7.88, df = 1, ΔOFV <10.8, df = 2; $p >0.005$). No significant difference was found among the mean clearance estimates in the three clinical centers. TBW (kg) was found to explain a significant proportion of the interindividual variability in the central (V_1) and peripheral (V_2) volumes of distribution. Approximately, 57% and 70% of the interindividual variability in V_1 and V_2, respectively, were explained by allometric scaling to a standard 70 kg individual. Neither age nor albumin, AAG or C_u had a significant effect on drug binding. Because C_u did not have an effect on binding, we further investigated the possibility that a fraction of individuals belong to a sub-population with concentration-

dependent binding of CBZ via the implementation of mixture models in NONMEM. The mixture model indicated that 99.5% of the studied population had a constant binding (i.e. constant F_u) of CBZ over the studied range of C_u. The final model included a race effect on the unbound clearance, and TBW as measured in kg on volumes of distribution. A backward elimination step was not performed since there was only one covariate effect per parameter included in the model.

Equation 4 describes the final model for unbound clearance of CBZ:

$$CBZ\ Unbound\ Clearance[i]\ (L/hr) = 11.2 \times (1.30)^{Race[i]} \qquad (4)$$

where Race[i] equals 1 if the patient is Caucasian or zero if the patient is African American.

Equations 5 and 6 describe the final model for the unbound volume of distribution in the central and peripheral compartment, respectively:

$$V_{i,1}(L) = 142.0 \times \left(\frac{WT_i}{70}\right) \qquad (5)$$

$$V_{i,2}(L) = 175.0 \times \left(\frac{WT_i}{70}\right) \qquad (6)$$

Where WT_i, is the i^{th} subject weight in kg.

Goodness of fit plots from the final model are shown in Figure 2.2 (A-H). Both unbound and total SL-CBZ predicted concentrations showed a close agreement with the observed values (Figure 2.2 A-D) and the conditional weighted residual plots showed lack of trend with respect to predicted concentrations and the time after dose (Figure 2.2 E-H).

2.3.3 The Nonparametric Bootstrap

The results of the bootstrap validation step are presented in Table 2.2. From the 1000 bootstrap runs, 921 successful runs were pooled for the final analysis. The estimates of the fixed effects and random effects obtained from NONMEM were all within 10% of the

bootstrapped means. Furthermore, the bootstrap 95% CI for all parameter estimates were comparable to NONMEM estimated CI.

2.3.4 Visual Predictive Check

The predictive check plots of unbound and total SL-CBZ are shown in Figure 2.3 (A-B). Of the observed data, 91.3% fit within the 5^{th} and 95^{th} percentiles of the simulated datasets. This may indicate that the model adequately described the overall trend and variability in the observed data.

2.4 DISCUSSION

The major results from this study of community dwelling adults and elderly epilepsy patients are that the unbound clearance of CBZ was dependent on race, but not on age, sex, smoking, plasma albumin or AAG concentrations. Total body weight explained 57% and 70% of the interindividual variability in the unbound central and peripheral volumes of distribution, respectively. Age, sex, smoking, plasma albumin and AAG concentrations had no effect on clearance, binding or distribution volumes. The stable-labeled intravenous dosing methodology enabled the estimation of the CBZ clearance and volumes of distribution.

We characterized, for the first time, the population PK of IV SL-CBZ under steady-state conditions in community-dwelling young adult and elderly populations. The use of an SL IV formulation coupled with a rich sampling schedule allowed the rigorous estimation of the absolute PK parameters under a clinically relevant setting without interruption of drug therapy. Unbound and total SL-CBZ concentration time profiles were best described by a linear 2-compartment model. Previous studies suggest that CBZ pharmacokinetics follow a one-compartment disposition behavior;[8,10,13-17,23] but none of these studies used IV CBZ. The high variability and prolonged absorption of CBZ from oral tablets and capsules may mask CBZ distribution and elimination characteristics in a sparse sampling setting.

The actual body weight was found to be a significant covariate for the volume of distribution in the central and peripheral compartments, whereas elimination clearance of

CBZ was found to be independent of body weight. The lack of a weight effect on clearance may be attributed to the relative homogeneity of body weight in the studied population (inter-quartile range 66 kg - 92 kg). Additionally, the effect of weight could be confounded by a variety of physical and hormonal factors.[25] Previous population pharmacokinetic studies reported weight as a significant covariate on CBZ clearance, but most of these studies included a wider range of body sizes than in our study.[10,18]

Covariate modeling results from our study suggested that CBZ PK were not influenced by age and sex. Regarding age, our results are in agreement with Hockings et. al., who reported an insignificant change in the PK of CBZ in five elderly compared with six young adults after a single oral dose of 400 mg.[17] In a study of 879 ambulatory patients, Graves et. al., showed that only subjects 70 years or older had a 25% reduction in oral CBZ clearance; however in that study, elderly patients only represented 1.7% of the population.[8] Similarly, in our study, the small number of elderly patients above the age of 60 (22/91) might have resulted in insufficient power to identify such an effect. A prolongation of GI transit, which may increase the bioavailability of CBZ could explain the results reported by Graves et al.[8] In addition to the results from the present study, aging was found to have an effect on the metabolism of another antiepileptic drug, phenytoin, in healthy younger adults (60-74 yrs).[26]

The effect of sex on the activity of CYP3A4 remains unclear; however, the enzyme is reported to have a greater activity in women than men for certain substrates.[27-29] Using a noncompartmental approach, Marino et. al., reported a significantly greater CBZ clearance in women than men aged less than 60 years ($p<0.007$).[21] In contrast, Furlanut et. al., found a significantly lower CBZ clearance ($p<0.005$) in girls than boys both with epilepsy, taking oral CBZ, and of comparable age and weight, possibly due to the inhibitory effect of estrogen on microsomal enzymes.[11] We found a mean reduction in the unbound CBZ clearance in young men compared to young women, however, the effect was reversed in the elderly, but the effects did not achieve a statistical significance.

Amongst all of the tested covariates, only race emerged as a predictor of CBZ unbound clearance, which was 30% higher in Caucasians compared to African Americans. Several

studies have found differences in clearance of specific drugs between Caucasians and African Americans.[21,30,31] Racial effects on drug disposition are thought to be caused by differences in drug metabolizing capacity. Perhaps the high incidence of the variant allele CYP3A4*1B in African Americans compared to Caucasians ($\chi^2 = 48.9$, $p < 0.001$)[32] partly explains the difference in clearance between the two groups. CYP3A4*1B is hypothesized to be associated with a decreased enzymatic activity.[33-35] which may confer a low clearance of CBZ in African Americans compared to Caucasians.

CBZ is approximately 75% bound to serum proteins, mainly to serum albumin and to a lesser extent to AAG.[36] Levels of the latter protein are elevated in inflammation, cancer and in elderly subjects.[37] We found no significant effect of albumin or AAG levels or age on CBZ free fraction. The patients in our study were relatively healthy with plasma albumin and AAG levels homogenously distributed within the normal range. This may explain the relatively small inter-individual variability (%CV~19%) encountered in the CBZ free fraction. Similarly, Koyama et. al., found no correlation between AAG level and CBZ free fraction.[12] The binding of CBZ was shown to be constant (F_u~0.25) over a range (0.1-1 mg/L) of unbound concentration. This finding does not exclude the possibility of a nonlinear binding for CBZ at higher concentrations than in our study.

To our knowledge, there are no reports of integrated modeling of unbound/total IV CBZ PK. Therefore, the current model for clearance was compared to other population CBZ PK studies involving oral CBZ taking into account an average estimate of bioavailability of 70%.[19,21] Based on the estimates of absolute clearance and bioavailability, the mean apparent CBZ unbound clearance would be 13.4 L/hr. In a study of Omani patients with epilepsy in which unbound CBZ clearance was determined by routine therapeutic drug monitoring, Deleu et. al. found a population mean apparent clearance of 13.2 L/hr.[13] Our results are in close agreement with that report. Furthermore, given a population estimate of 0.25 for the fraction unbound in plasma (our study), the total clearance of CBZ was estimated to be 3.35 L/hr which is consistent with estimates of the mean CBZ clearance reported in other studies.[10,18,38] The standard diagnostic plots suggested that the final model adequately described both unbound and total SL-CBZ data. The observed trend in the residuals at low prediction values or late sampling times (Figure 2.2 G and H) might

not be influential due to the possible low accuracy of the analytical assay at such low concentrations and potential errors in recording late sampling times.

In conclusion, we have characterized the steady-state compartmental PK of unbound and total CBZ using stable-labeled intravenous formulation given to patients with epilepsy on maintenance CBZ regimens. We found no effect of aging in relatively healthy young-old (60-74 yrs) patients. In contrast, the influence of race on CBZ clearance was highly significant and warrant further investigation. Results from our study may support race specific dosing for CBZ where an African American patient would receive, on average, 70% of the standard dose prescribed for a Caucasian. The satisfactory performance of the proposed population model may justify its applicability in estimating the steady-state PK parameters for CBZ.

Table 2.1. Baseline Characteristics of Patients Included in the Model Building Process.

Characteristic	Mean ± SD or Number
Weight (kg)	80.6 ± 19.4
Body Surface Area (m^2)	1.9 ± 0.2
Lean Body Weight (kg)	55.4 ± 11.3
Ideal Body Weight (kg)	63.7 ± 10.3
Age (years)	46.1 ± 14.9
Young adults (Age <60)	
Number	91
Median age (range)	42 (19-59)
Sex [Women/Men]	46/45
Race [Caucasian/African American]	49/42
Elderly (Age ≥60)	
Number	22
Median age (range)	66 (60-87)
Sex [Women/Men]	7/15
Race [Caucasian/African American]	21/1
Women	
Number	53
Median Age (range)	41 (20-72)
Age group [age<60/age≥60]	46/7
Race [Caucasian/ African American]	31/22
Men	
Number	60
Median Age (range)	48 (19-87)
Age group [age<60/age≥60]	45/15
Race [Caucasian/ African American]	39/21
Total protein concentration (mg/dL)	7.0 ± 0.5
Albumin concentration (mg/dL)	4.0 ± 0.4
Alpha 1-acid glycoprotein concentration (mg/dL)	79.7 ± 22
Sex [Women/Men]	53/60
Race [Caucasian/African American]	70/43
Smoking history [Smokers/Nonsmokers/Missing]	22/47/44
Alcohol consumption [Consumers/Non-consumers/Missing]	24/42/47
Grape fruit consumption [Consumer/Non-consumers]	71/42

Table 2.2. Final Model Parameter Estimates and 95% C.I. from the Original Dataset and Bootstrap Analyses

	NONMEM Analysis	**Bootstrap Analysis**		
Parameter	**Estimate (% SE)**	**95% CI**	**Median**	**95% CI**
CL_{un}(L/hr)	11.2 (5.5)	10 - 12.4	11.2	10.3 - 12.3
$V_{1,un}$ (L/70kg)	142 (4.8)	128.6 - 155.4	143	127 - 179
Q_{un} (L/hr)	444 (15.8)	306.4 - 581.6	429	189 - 611
$V_{2,un}$ (L/70kg)	175 (4.2)	160.5 - 189.5	175	131 - 191
F_u	0.25 (2.1)	0.24 - 0.26	0.25	0.24 - 0.26
θ^{RACE}	1.30 (8.3)	1.08 - 1.51	1.30	1.14 - 1.47
Interindividual variance (% SE)				
IIV of CL_{un}	0.104 (28.5) CV% = 32.2	0.046, 0.162	0.101	0.065, 0.139
IIV of $V_{1,un}$	0.046 (29.8) CV% = 21.5	0.019, 0.073	0.052	0.018, 0.127
IIV of Q_{un}	1.78 (21.7) CV% = 133	1.02, 2.54	1.72	0.146, 2.52
IIV of $V_{2,un}$	0.055 (33.5) CV% = 23.5	0.019, 0.092	0.051	0.029, 0.149
IIV of F_u	0.036 (13.4) CV% = 18.9	0.026, 0.045	0.043	0.027, 0.045
Residual variance (% SE)				
RUV_{un}, Prop.	0.032 (16.4) CV% = 17.8	0.022, 0.042	0.031	0.022, 0.042
RUV_{Tot}, Prop.	0.024 (14.4) CV% = 15.5	0.017, 0.031	0.021	0.018, 0.031
RUV_{Tot}, Additive.	0.002 (19.9)	0.001, 0.003	0.002	0.001, 0.003
	SD (mg/L) = 0.05			

CI, confidence interval; CL_{un}, unbound carbamazepine clearance estimated for an African American individual (considered to be the reference group); $V_{1,un}$, unbound central volume of distribution; Q_{un}, unbound intercompartmental clearance; $V_{2,un}$, unbound peripheral volume of distribution; F_u, fraction unbound; θ^{RACE}, race effect, has a power of 1 if the patient is Caucasian, and a power of zero if the patient is African American; IIV, interindividual variability; %CV, percentage coefficient of variation; RUV_{un} and RUV_{Tot} are residual unexplained variability in the unbound concentration and total concentration, respectively, expressed as a proportional error variance.

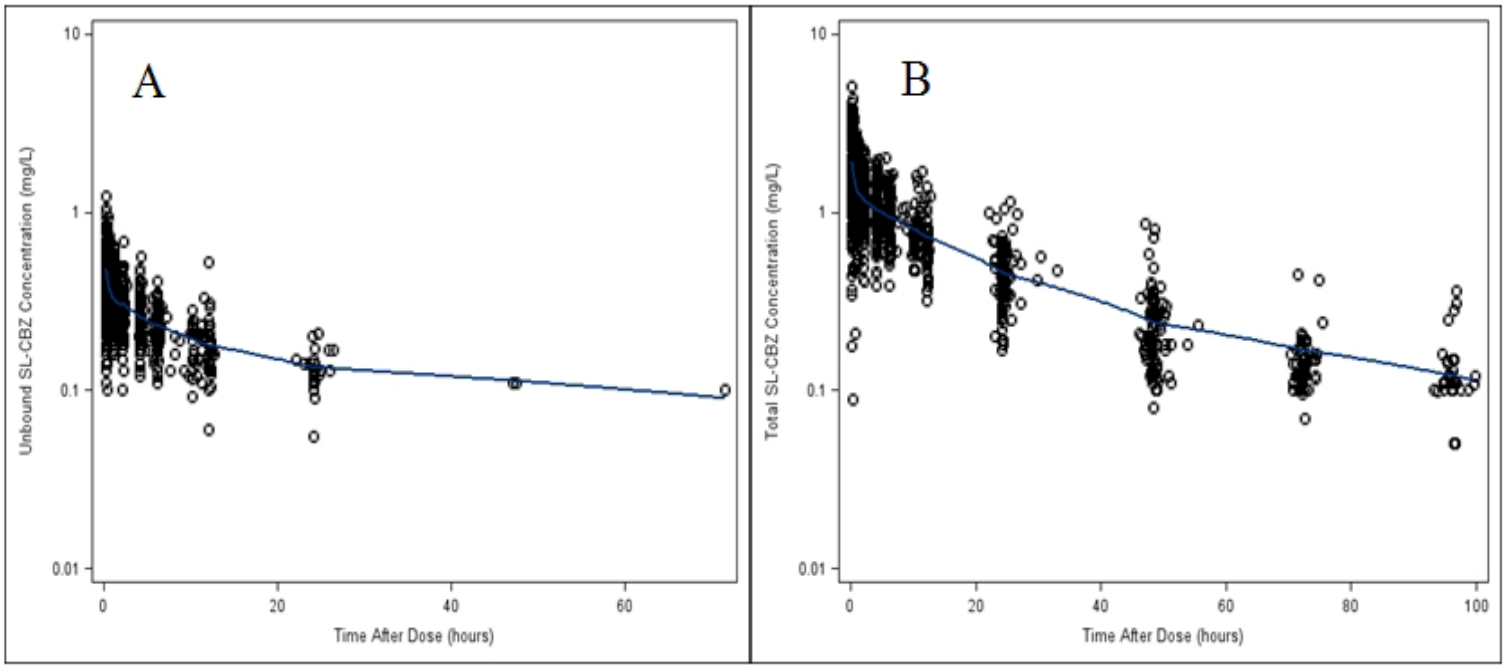

Figure 2.1. A) Scatter plot of observed unbound SL-carbamazepine concentration versus time after dose. B) Scatter plot of observed total SL-carbamazepine concentration versus time after dose. The line through the data represents a Locally Weighted Scatterplot Smoother (LOESS) fit to the data.

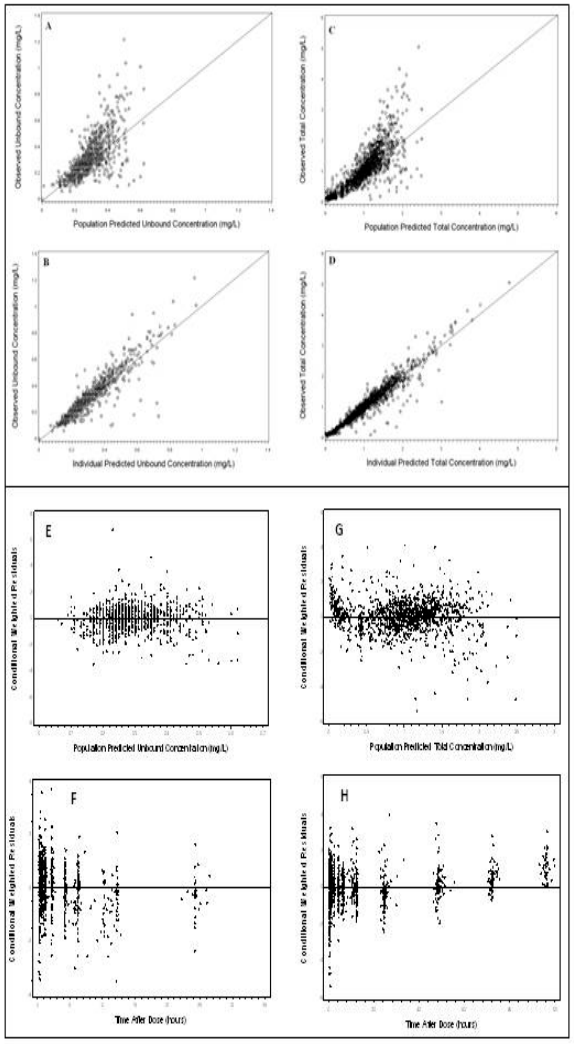

Figure 2.2. Goodness of fit plots for the final population pharmacokinetic model. (A) Identity plot of observed versus population predicted unbound concentration; (B) Identity plot of observed versus individual predicted unbound concentration; (C) Identity plot of observed versus population predicted total concentration (D) Identity plot of observed versus individual predicted total concentration (E) Scatter plot of conditional weighted residuals (CWRES) versus population predicted unbound concentration (F) Scatter plot for CWRES versus time after dose for unbound concentration fit (G) Scatter plot for CWRES versus population predicted total concentration and (H) Scatter plot for CWRES versus time after dose for total concentration fit.

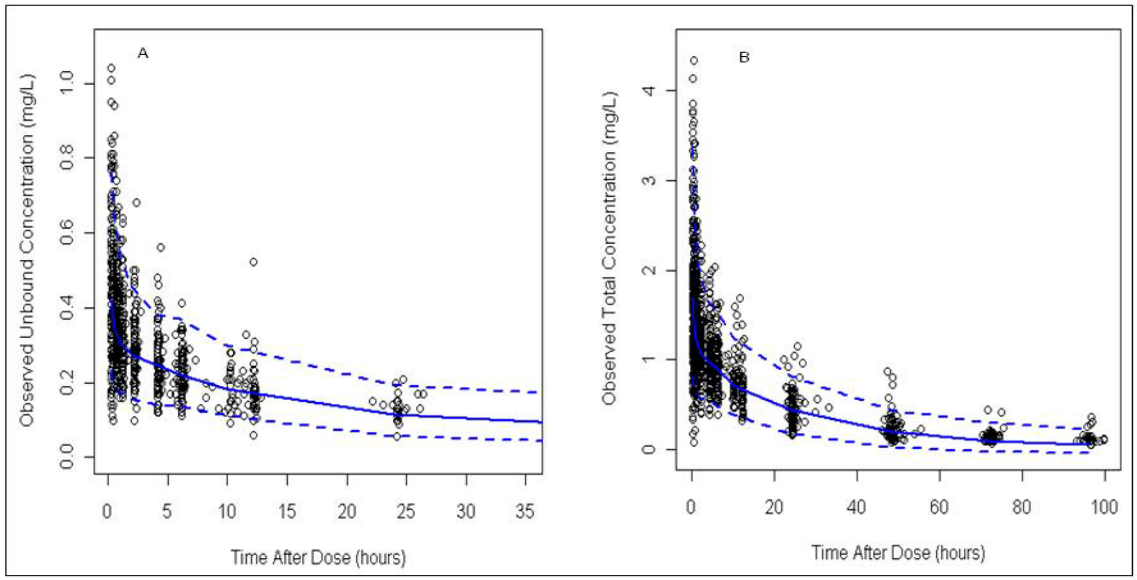

Figure 2.3. Visual predictive check plots of observed unbound (A) and total (B) SL-CBZ concentrations (open circles), median (solid line), and 5^{th} and 95^{th} quantiles (dashed lines) of 1000 simulated data sets.

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Chapter III

Population Pharmacokinetics and Saturable Absorption of Gabapentin in Nursing Home Elderly Patients

3.1 INTRODUCTION

Approximately 10% of nursing home patients are prescribed anti-epileptic drugs (AEDs) for both treatment of epilepsy and other indications such as neuropathic pain.[1,2] Chronic pain affects about 50% of community-dwelling elderly and over 80% of nursing home residents. [3-6] Despite the high prevalence of pain and the widespread use of AEDs in nursing home residents, little information is available on the pharmacokinetics of AEDs in this patient population. While age-related changes in organ functions and body composition may impose substantial differences in the pharmacokinetics of AEDs,[7,8] limited studies in community-dwelling elderly patients found advancing age to have no effect on population clearance or protein binding of some AEDs.[9,10] Whether these findings can be extrapolated to nursing home elderly patients is unknown, as the latter populations are different from their community dwelling peers in many ways: nursing home elderly patients are physically frailer, of older age, more cognitively impaired, suffering more comorbidities, and receiving more medications than community-dwelling elderly patients.[11-13] These factors can induce more inter and intraindividual variability in the pharmacokinetics of AEDs and limit the ability to extrapolate findings from the community-dwelling older people to nursing home elderly patients.

The pharmacokinetics of gabapentin [GBP; an AED that is approved for the adjunctive treatment of partial seizures in adults and children (≥ 3 years old), and for the treatment of chronic and neuropathic pain] has previously been studied in adult and community-dwelling elderly patients with epilepsy.[10,14-16] However, no information is available to guide dosing of GBP in nursing home elderly patients. GBP exhibits favorable pharmacokinetic characteristics as it is not significantly metabolized by the liver and has low protein binding.[17] Therefore, GBP has no clinically relevant interactions with other drugs.[18] However, the PK of GBP is complicated by a dose-dependent saturable absorption observed across the usual clinical dose range (up to 2400 to 3600 mg/d). Thus upon increasing dose, steady-state plasma concentration increases in a less-than-dose-proportional manner due to the saturation of the $_{L}$-amino acid transport system across the gut.[14,19]

GBP is excreted unchanged in the urine and dosage adjustment is necessary in patients with renal impairment. A previous study of single-dose pharmacokinetics of GBP in healthy subjects (20-78 years) recommended a reduction in GBP dosage in elderly patients due to reduced renal function.[15] Because of its hydrophilic nature, GBP would be predicted to have a limited distribution in the elderly as a result of decreased total body water and lean body mass. Similar to the decreased absorption of vitamin B_{12}, iron and glucose – accomplished by active transport mechanisms- in the old persons, systemic bioavailability and the saturable absorption profile of GBP is likely to be altered in the elderly patients due to a reduced gastric emptying rate and absorptive capacity of the small intestine.[20-22] This study presents the population analysis of GBP in nursing home elderly patients with chronic pain performed to characterize the PK of GBP and identify important physiologic determinants of GBP disposition. Furthermore, a model-based simulation analysis was conducted to investigate the effect of modifying oral administration schedules on the absorption of GBP in this patient population.

3.2 MATERIALS AND METHODS

3.2.1 Subjects

The University of Minnesota's institutional review board approved the study. The study was explained to all subjects and a consent form was signed by the subject or their designated guardian before participating. Elderly patients (older than 60 years) were recruited from 4 nursing homes located in Minnesota. Patients received GBP mainly for the treatment of chronic pain conditions. Patients who were on the same dose of GBP for at least 4 weeks (were assumed to be at steady-state), in the facility for at least 2 months, and on a stable dose of co-medications were included. Comatose subjects or those with unstable medical conditions that would compromise their survival throughout the study period were excluded.

3.2.2 Study Design and Collection of Samples

Each resident was followed for a period of approximately 9 months. The study was designed to include 4 observation visits per subject on a stable dose of GBP. If a dose

change occurred before the 4th visit, subjects were allowed to restart so that 4 observations could be obtained at a particular dose. At each visit, blood samples were collected for the measurement of GBP concentration and the time recorded to determine the amount of time after the dose. In addition, basic clinical lab measures (blood chemistries and kidney and liver function tests) were obtained. Information about date of birth, race, ethnicity, sex, height, weight, and medical history was collected at the screening period.

3.2.3 Measurement of Gabapentin Concentrations

Plasma concentrations of GBP were analyzed by an LC-MS detection method. The assay was validated in our laboratory to simultaneously monitor two polar gamma-aminobutyric acid (GABA) derivative AEDs in the same sample: GBP and pregabalin. For GBP, $^{2}H_4$-Gabapentin (GBP-d_4, Toronto Research Chemicals, North York, Canada) was used as the internal standard. Patient samples were prepared using solid phase extraction (SPE) method. The SPE column (1 mL of Strat-X-CW 33 uM 30 mg/ 1mL; Phenomenex, Torrance, CA) was pretreated with 100% methanol followed by Millipore water and centrifuged at low speed (500 rpm) after each treatment. A mixture of 50 μL of patient plasma and 400 μL of internal standard were loaded to the pretreated SPE column, centrifuged at 500 rpm for 30 seconds and washed with 500 μL Millipore water followed by a one-minute centrifugation at 500 rpm. Samples were then eluted in a three-step process with 500 μL of 2% formic acid in methanol, dried under nitrogen at 36 ^{0}C, reconstituted in 1000 μL of the injection buffer (methanol: formate buffer 20:80), and centrifuged at 10,000 rpm for 10 minutes. The mobile phase consisted of a mixture of two components: the first included 10 mM formate buffer with 1.25 mM heptaflourobutyric acid (HFBA; pH 3.0), while the second comprised 100% methanol with 1.25 mM HFBA, and was run at a constant flow rate (0.4 mL/min) with a gradient design that varied the percentage of the second solution from 15% to 45% over a time period of 7 minutes. All samples from an individual patient were run at the same time along with 6-concentration standard curve (linear range 0.27 – 21.35 μg/mL) and low, medium and high concentrations of quality control samples. The assay had an acceptable

limits of precision with %CV <5% at the upper limit of quantification and <10% at the lower limit of detection.

3.2.4 Pharmacokinetic Analysis

The population PK analysis consisted of nonlinear mixed effects modeling in NONMEM (version 7, ICON Development Solutions, Ellicot City, MD, U.S.A.). A one-compartment model was fitted to the data. The model was parameterized in terms of clearance (CL), volume of distribution (V) and a first-order absorption rate constant (K_a). The between subject variability was estimated through an exponential error model and expressed as a coefficient of variation (CV). Different models were tested to account for the residual unexplained variability including an exponential model, proportional model, additive model, and combined proportional and additive model.

Covariate modeling was guided by visual examination of the plots of variability in the PK parameters versus covariate values, improvement in the model diagnostic plots (observed versus predicted GBP concentration and conditional weighted residuals versus time) after inclusion of the covariate, plausibility of the parameter estimates, and the statistical significance using a likelihood ratio test (LRT; forward inclusion, χ^2, $p \leq 0.05$, df = 1; backward elimination, χ^2, $p \leq 0.01$, df = 1).

In this study, estimated glomerular filtration rate (EGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) equation which takes into accounts the patient's serum creatinine, age, sex and race.[23,24] In addition, we estimated renal function using the Cockcroft-Gault (CG) equation.[25] Both linear and power functions were tested for modeling the effect of measures of renal function (EGFR and CG-based CLcr) on GBP CL and the results were compared. Sex, weight and age were tested sequentially for their independent effect on CL after accounting for the effect of renal function. Finally, the effect of increasing the GBP dose on the extent of absorption was evaluated by testing for the significance of a saturable absorption profile. In this model, both simple and sigmoidal inhibitory I_{MAX} functions were tested in modeling the bioavailability (F) of GBP as a function of dose.

3.2.5 Evaluation of the Pharmacokinetic Model

The PK model was qualified by means of standardized visual predictive check (SVPC) where datasets (n=1000) were simulated using the final model, and the average percentiles ($P_{i,j}$) of the j^{th} concentration for the i^{th} patient in the marginal distribution of model-simulated concentrations were plotted against time, dose and covariate values. Moreover, the precision of the parameter estimates from the final model was determined using bootstrap analysis.

3.3.6 Simulation of Average Steady State Concentration of Gabapentin

The final PK model was used to simulate the average steady state GBP concentration (C_{ave}) for a typical nursing home patient with an EGFR of 69 mL/min. A range of GBP doses was considered (100 -1000 mg) and a total of 1000 subjects were simulated for each dose. The median of the C_{ave} was calculated and plotted against the dosing regimens of GBP.

3.3 RESULTS

A total of 114 plasma concentrations obtained from 30 patients were included in this analysis. Patients received GBP for the treatment of pain conditions (a neck and shoulder pain, multiple joint pain, polymyalgia rheumatica, and neuropathic pain). Analgesic comedications included acetaminophen, aspirin and opioids (hydromorphone, oxycodone, methadone, tramadol and fentanyl patches). The characteristics of the study population, distribution of kidney function estimates and total daily doses of GBP are shown in table 1.

3.3.1 Pharmacokinetic and Covariate Models

The PK model was a one-compartment model with first-order absorption and elimination. Residual unexplained variability was described by a proportional error model. When plotted against GBP dose, the random effects on F revealed a trend of a sigmoidal inhibitory profile (Figure 1). Upon model fitting, the sigmoidal I_{MAX} model was less sensitive to changes in initial estimates and produced more plausible parameter estimates

than all other tested models (linear, simple I_{MAX}, etc). In addition, the inclusion of the effect of GBP dose on F resulted in a drop of 11.3 points in the objective function value (OFV; $p<0.05$, df =3) when compared to the base PK model with a constant F of 1.

A scatter plot of random effects of CL against EGFR is shown in Figure 2. This plot shows a strong correlation between kidney function and GBP CL. A similar type and pattern of relationship between the random effects of GBP CL and the CG-based CLcr were observed (results not shown). When modeled, the effect on GBP CL using either estimates of renal function did not result in changing the model structure or the calculated GBP CL values at different levels of renal function. The calculated GBP clearances were within 20%, 2% and 1% of the MDRD-based values at the low, moderate and high levels of renal functions, respectively. The MDRD-based GFR was thus used for further model development. Accounting for the effect of EGFR (ml/min) on the GBP CL resulted in a significant drop in the OFV (ΔOFV=51.7, $p<0.0001$), reduced the intersubject variability on CL by 50% and significantly improved the model fit diagnostics. The power model fit had lower Akaike information criterion (AIC; 230.9) and more stability in convergence compared to the linear model (232.0), therefore, the power function was eventually selected for modeling the effect of EGFR on GBP CL.

After adjusting for the effect of renal function, GBP CL was not further affected by age, sex, body weight or other body size measures. Final model equations, parameter estimates and bootstrap confidence intervals are shown in Table 2. The typical value of CL in a nursing home elderly patient with an EGFR of 69 ml/min was 4.62 L/hr. Furthermore, the model estimated a maximum absolute reduction (I_{MAX}) in F of 54% (95% CI 26%, 81%) and a dose that produces half of the maximum saturation (ID_{50}) of about 486 mg (300, 668). None of the tested covariates including weight, body size measurements, age or sex were found to significantly affect the volume of distribution.

Bootstrap confidence intervals of the fixed and random effects parameter estimates tended to be somewhat wider than the NONMEM produced confidence intervals (Table 2). This may indicate some imprecision in the estimation of the model parameters. This is probably due to the sparseness of the data collected in this study and the limited

information available in support of simultaneous estimation of the model parameters. Nevertheless, inclusion of EGFR on CL and dose on F led to a substantial improvement in the visual appearance of observed versus population predicted concentrations and conditional weighted residuals versus population predicted concentrations (Figure 3), thus these covariates were retained in the final PK model.

3.3.2 Model Qualification

The SVPC plots of $P_{i,j}$ against time after dose, GBP dose and EGFR (ml/min) are shown in Figure 4. It is observed that the $P_{i,j}$ values are uniformly distributed between 0 and 1 over time or covariate values with a majority of the $P_{i,j}$ values falling within the 5^{th} and 95^{th} quantiles. Therefore the final model was considered to adequately describe both fixed and random effects and the PK profile of GBP to be reasonably well defined by the final PK model with good predictive performance.

3.3.3 Effect of Dose-dependent Bioavailability on Average Steady State Concentrations of Gabapentin

The simulated median C_{ave} of GBP versus dosing schedule is shown in Figure 5. In these simulations, various dosing regimens were examined to deliver the same total daily doses of GBP. Higher C_{ave} concentrations were observed with smaller doses of GBP given on more frequent dosing schedules. Furthermore, the effect of frequent GBP administration on C_{ave} was more pronounced at higher (600 – 1000 mg) than lower GBP doses (200 – 400 mg). Smaller doses given more often resulted in a relatively higher C_{ave} than large once daily doses of GBP.

3.4 DISCUSSION

The major results from this study of GBP PK in nursing home elderly patients are that the clearance of GBP is dependent on kidney function with no additional effect of age, sex or body weight. Dose-dependent bioavailability of GBP was demonstrated, and the saturable absorption profile was described by a sigmoidal I_{MAX} model. The estimated ID_{50} was 450 mg and found to be lower than previous estimates in younger adults. Model-based simulations suggested a substantial increase in systemic exposure with the administration

of high total daily dose (≥600mg) as smaller doses of GBP given more often due to the increase in oral bioavailability.

With the exception of the mean body weight (85.2 kg) and BMI (30.5 kg/m^2), the demographic features of this population were consistent with the previously reported characteristics of nursing home residents.[28,29] Using recently proposed gender-specific cut off points of BMI in the elderly (BMI > 27 kg/m^2 for men and ≥ 25 kg/m^2 for women), about 63% of our nursing home sample were identified as obese.[30] Previous studies have observed lower ranges of both mean body weight (62.1 kg to 68.6 kg) and prevalence of obesity (21% to 25%) in the nursing home elderly population.[31-37] Given the complexity of medical conditions, drug treatments and age-related physiological changes in the nursing home residents, several factors might contribute to this discrepancy including treatment with GBP. GBP at dose ranges of 900-1200 mg and 1200-2400 mg was found to be associated with a modest incidence of weight gain in adult patients with migraine (9%) and fibromyalgia (8%), respectively.[38,39]

As expected for a drug cleared primarily by renal excretion, a strong association between the CL of GBP and estimated GFR was demonstrated. A wide range of estimated GFR was represented in this study (13.8 – 109.9 mL/min/1.73 m^2) with a majority of the estimates (75%) being within the range of mild to moderately decreased GFR and only 26% representing either normal (16%) or severely impaired (9%) GFR. On average, nursing home elderly patients had a mild decrease in EGFR as demonstrated by a mean of 62.4 mL/min/1.73 m^2. GBP clearance estimates for a nursing home elderly with low (20 mL/min), moderate (50 mL/min) and normal (90 mL/min) GFR were 1.59, 3.48, and 5.78 L/hr, respectively. These values are slightly lower than clearances of 5.7 and 8.5 L/hr reported in community-dwelling elderly patients with moderate and normal renal functions, respectively.[10]

Similarly, our estimate of the volume of distribution (0.4 L/kg) was found to be lower than previous reports in community-dwelling elderly patients (1.36 L/kg), healthy volunteers (0.6 L/kg) and patients with chronic neuropathic pain (0.91 L/kg).[10,40,41] Polar drugs, such as GBP, tend to have a smaller volume of distribution in elderly patients than

younger adults due to age-related changes in body composition.[7] The expected effect of a decrease in the volume of distribution is a reduction in half-life ($T_{1/2}$) and a possible increase in GBP peak levels in older subjects compared to younger adults.[8] A retrospective study of GBP trough concentrations collected from 66 subjects, aged 5-84 years found elderly patients (>65 years) with normal renal function to have a two-fold higher GBP concentration-to-dose-ratio than that of younger adults and recommended a reduction in GBP dose by half to achieve similar concentration.[42] We, however, calculated GBP half-life in a typical nursing home elderly resident to be ~ 5.2 hours; in agreement with previously reported $T_{1/2}$ range of 5.9 to 9.2 hours in adults and healthy young-old subjects (18 to 78 years).[15,16] The small effect of the decreased volume of distribution on half life may, in part, be due to the lower renal clearance of GBP in nursing home than healthier elderly patients.

Gabapentin is absorbed from the gut by a saturable $_L$-amino acid transporter which is hypothesized to be responsible for the dose-dependent bioavailability of GBP.[19,43] Other mechanisms of absorption could be involved at higher doses (up to 6000 mg/day) as both the area under the plasma concentration-time (AUC) and serum concentration continue to linearly increase at such high doses.[44,45] In agreement with that, we found the decrease in F of GBP to be adequately represented by a sigmoidal I_{MAX} function with an ID_{50} of 468 mg and a maximum absolute reduction of about 54%. Interestingly enough, the estimated ID_{50} in our study is markedly lower than previous estimates of 700 mg and 1120 mg reported for healthy volunteers and younger adult patients with neuropathic pain, respectively.[14,40,41] A reduction in gastric-emptying rate and absorptive capacity of the small intestine in elderly patients might contribute to saturation of absorption at such low doses of GBP in this population.[46,47]

Model-based simulation of C_{ave} in this population revealed that dividing daily doses into higher frequency smaller doses may result in an increase in GBP bioavailability. The effect of frequent administration was more apparent at high doses compared to low doses of GBP. For instance, administering a dose of 200 mg twice daily resulted in an increase of 15% in C_{ave} when compared to a once daily dose of 400 mg. On the other hand, a 57% increase in C_{ave} was obtained by dividing the dose of 600 mg to 300 mg given as b.i.d

when compared to dosing 600 mg of GBP once daily. Further divisions of this dose to a 200 mg given every 8 hours resulted in a small increase in C_{ave} (5% increase). Similarly, increasing the dose frequency to a thrice daily dose of 300 mg maximized the benefit by providing a 98% increase in C_{ave} as compared to giving a dose of 900 mg every 24 hours. Hence, clinicians need to be aware that a desired increase in steady state GBP concentration for an elderly patient may not necessarily involve increasing the total daily dose; rather alteration of drug administration frequency may be more beneficial.

While increasing the frequency of doses seems to be of clinical and economic value, in that an increase in GBP efficacy and systemic exposure is expected with no increase in total dose or medication expense, caution is needed when recommending such a dosing strategy for the elderly patients. This is because the gain in increasing systemic drug exposure may be counteracted by complicating the GBP administration schedule. Indeed, Cramer et. al. calculated that the odds of missing an AED dose increased by 27% for each increase in the number of times per day AEDs were taken.[48] Nonetheless, frequent dosing is unlikely to reduce compliance or complicate medication schedule in nursing home residents. Patients in the nursing home setting are routinely assisted by the facility's staff and caregivers for taking their medications, and often maintained on a long list of co-medications that are administered frequently during the day.[49]

In conclusions, this analysis characterized the population PK of GBP in nursing home elderly patients receiving GBP mainly for pain conditions. Similar to published PK findings in other populations, GBP CL was strongly dependent on the glomerular filtration rate and a dose adjustment based on the stage of kidney functions may need to be considered in this patient population. The bioavailability of GBP decreased in a nonlinear sigmoidal I_{MAX} manner with increasing GBP dose. Model-based simulations indicated that a substantial increase in C_{ave} is expected with the administration of high total daily dose ($\geq$600mg) as smaller doses of GBP given more often due to the increase in oral bioavailability.

Table 3.1. Summary of the Subject Characteristics and Variables Included in the Model Development Dataset

Characteristic	Mean ± SD Median (range) Number
Number of subjects Number per nursing home (I/II/III/IV)	30 8/14/6/2
Weight (kg)	85.2 ± 26.5 81.5 (54.4 – 168.3)
Height (cm)	167.3 ± 10.03 164.9 (154.9 – 190.5)
BSA (m^2)	1.92 ± 0.27 1.87 (1.56 – 2.6)
LBW (kg)	50.6 ± 11.3 46.9 (36.4 – 79.1)
Body Mass Index (kg/m^2)	30.5 ± 9.7 28.2 (18.2 – 59.9)
Age (years)	76.3 ± 10 75.5 (61 – 95)
Sex (Men/Women)	7/23
Race (Caucasian/African American)	28/2
Total Daily Dose of GBP (mg)	798.2 ± 670.5 500 (100 – 2400)
Doses per day	2.4 ± 0.94 3 (1 – 4)
EGFR (ml/min/1.73 m^2)[a]	62.4 ± 22.6 62.4 (13.8 – 109.9)
EGFR (ml/min)[b]	68.73 ± 28.05 65.16 (18.31 – 146.98)
CLcr (ml/min)[c]	68.04 ± 36.28 56.69 (26.5 – 175.5)

BSA is body surface area calculated using DuBois, et al's formula,[26] and LBW is lean body weight calculated using Sarayut, et al's model.[27] [a]EGFR is the estimated glomerular filtration rate calculated using the abbreviated MDRD study equation.[23,24] [b]EGFR (ml/min) is the individualized GFR estimate calculated by multiplying the EGFR by the individual's BSA and dividing by 1.73 m^2. [c]CLcr is creatinine clearance based on the C-G equation.[25]

Table 3.2. Final PK Model Equations, Parameter Estimates and Bootstrap Confidence Intervals (C.I.)

$$CL_i = \theta_1 \times \left(\frac{EGFR\,(\text{ml/min})}{69\,\text{ml/min}} \right)^{\theta_2} \times \exp(\eta_i)$$

$$F = 1 - \left(\frac{I_{MAX} \times DOSE^{HILL}}{ID_{50}^{HILL} + DOSE^{HILL}} \right)$$

	NONMEM Analysis		Bootstrap Analysis	
Parameter	Estimate (% SE)	95% CI	Median	95% CI
θ_1 (L/hr)	4.62 (10.3)	3.69 – 5.55	4.67	2.23 – 5.47
θ_2	0.86 (13.5)	0.64 – 1.09	0.88	0.63 – 1.21
V_c (L)	34.8 (35.1)	10.9 – 58.7	24.5	7.89 – 85.2
K_a (hr^{-1})	0.17 (30.8)	0.07 – 0.27	0.16	0.04 – 0.42
I_{MAX}	0.54 (25.7)	0.27 - 0.81	0.52	0.10 – 1.10
ID_{50} (mg)	486 (19.1)	304 - 668	428	101 – 751.75
HILL	4.63 (61.1)	-0.92 – 10.2	6.12	0.52 – 63.9
Interindividual variance (% SE)				
IIV of CL	0.04 (30.6) CV% = 21.1	0.02, 0.07	0.04 CV%=20%	0.003, 0.25
IIV of V_c	0.85 (183) CV% = 92.4	-2.2, 3.91	0.38 CV%= 61.6%	0.00001, 3.99
Residual variance (% SE)				
RUV, Prop.	0.06 (23.2) CV% = 24.8	0.03, 0.09	0.06 CV%= 24.5%	0.04, 0.09

%SE, percent standard error; V_c, central volume of distribution; K_a, first order absorption rate constant; IIV, interindividual variance; RUV, residual unexplained variance.

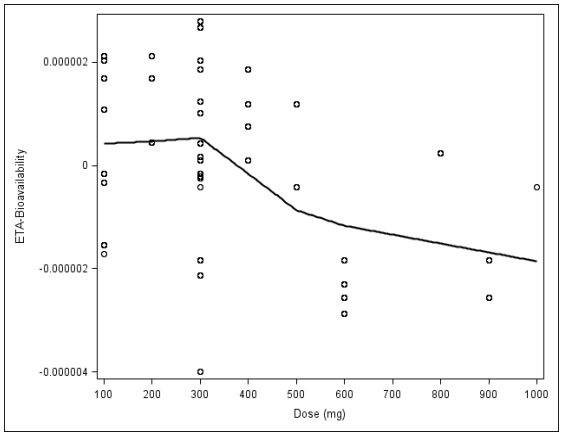

Figure 3.1. Exploratory plot of ETA on bioavailability versus dose of GBP suggesting a trend of a sigmoidal inhibitory relationship. The line through the data is a LOESS smooth.

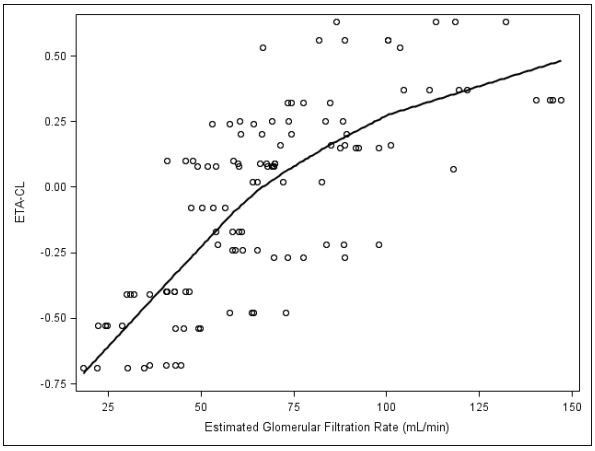

Figure 3.2. Exploratory plot of ETA on clearance of GBP showing a strong nonlinear association with glomerular filtration rate. The line through the data is a LOESS smooth.

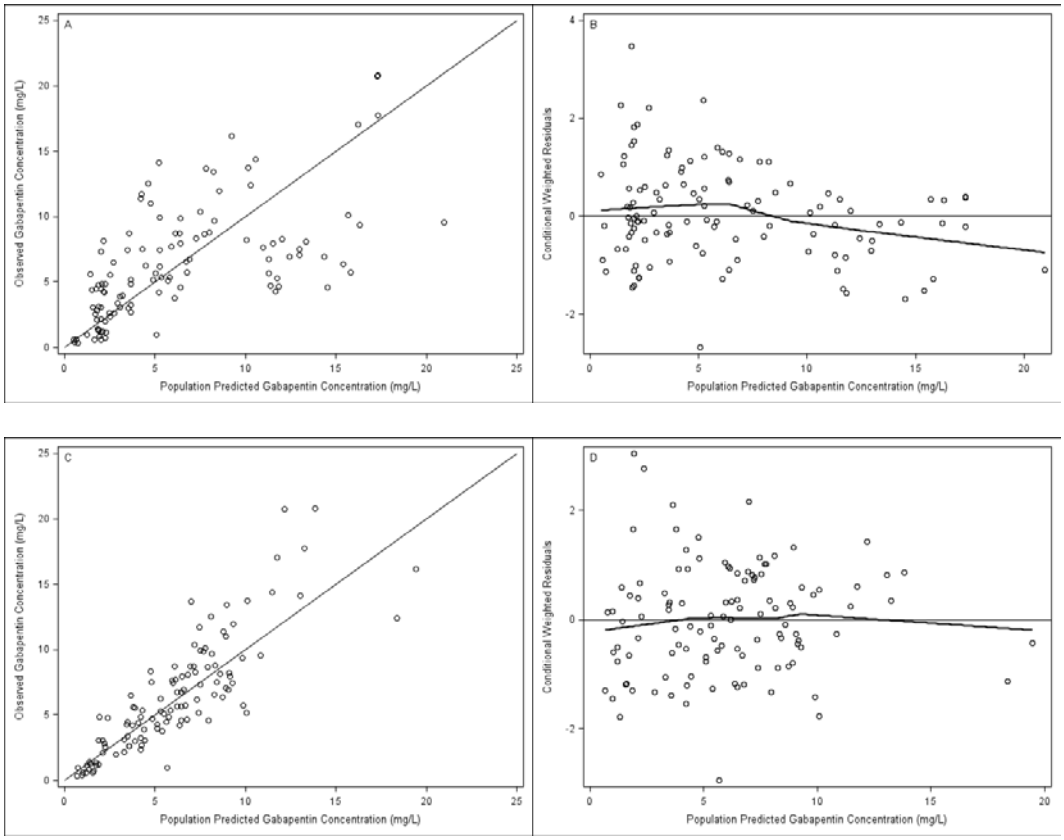

Figure 3.3. Goodness-of-fit plots for the base and final population PK model. Observed GBP concentration and conditional weighted residuals versus population predicted concentrations from the base model (A&B) and final model (C&D).

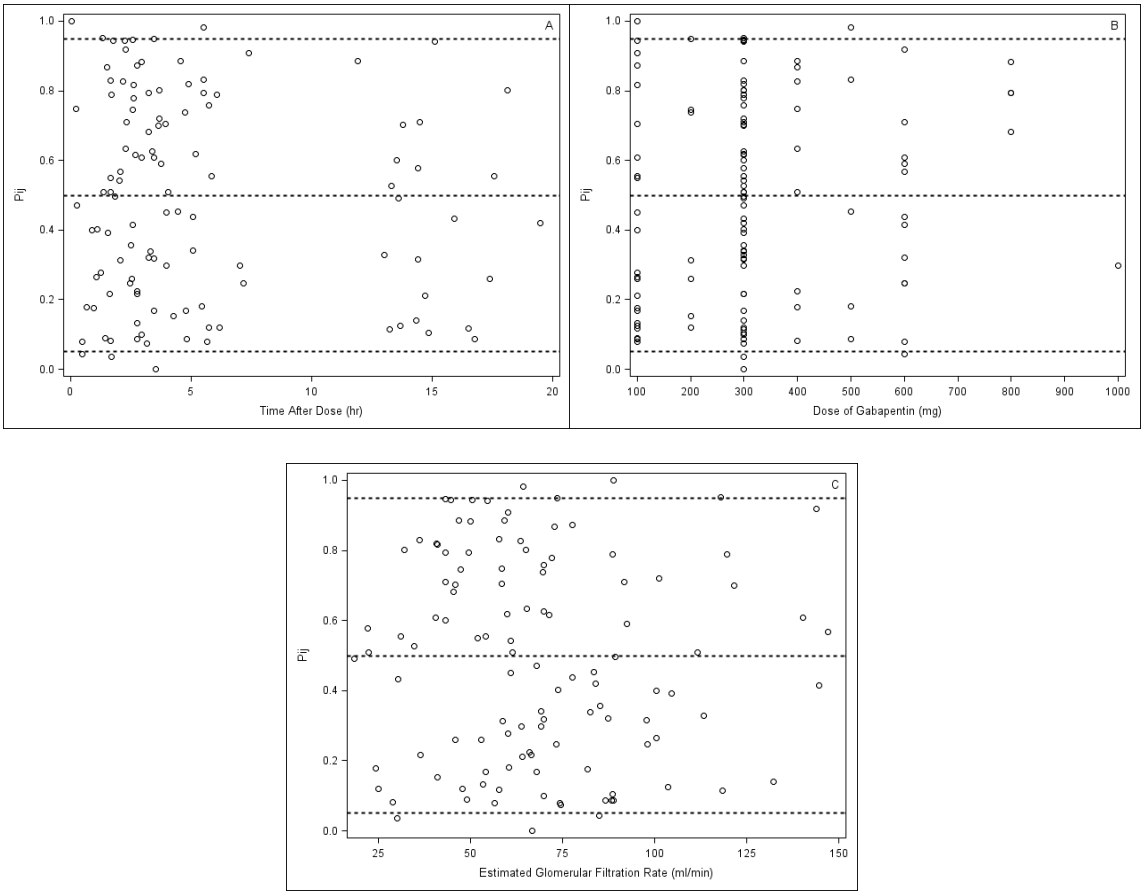

Figure 3.4. The standardized visual predictive check plots of the calculated percentiles for each observation (P_{ij}) versus time after dose (A), dose of gabapentin (B) and estimated glomerular filtration rate (C); dashed lines are 5^{th}, 50^{th}, and 95^{th} percentiles of model-predicted P_{ij} (from bottom to top).

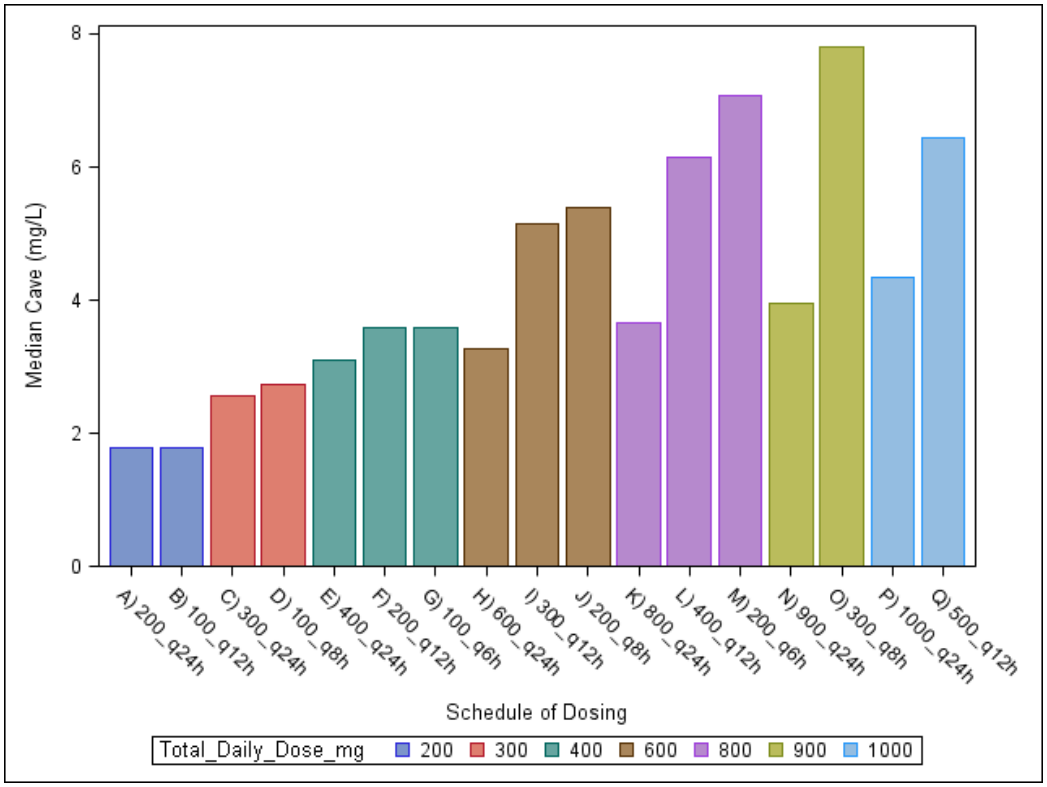

Figure 3.5. The effect of dose frequency on the average steady state concentration of GBP.

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CHAPTER IV

Pharmacokinetic-Pharmacodynamic (PK-PD) Modeling of Intravenous and Oral Topiramate and its Effect on Phonemic Fluency in Adult Healthy Volunteers

4.1 INTRODUCTION

Topiramate (TPM), 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate, with indications as monotherapy for recently diagnosed partial epilepsy, add-on treatment for resistant partial-onset seizures, and prophylactic treatment for migraine, is also being prescribed for a range of other conditions including obesity, pain, bipolar disorder and alcoholism.[1,2] TPM has been widely reported to cause adverse cognitive effects specifically related to working memory and verbal fluency in healthy volunteers and patients with epilepsy and migraine.[3-5] The incidence of cognitive complaints across studies of both healthy volunteers and patients is highly variable (3-44%).[1,4-8] While this variability in response has been attributed to dose, rapid titration, polytherapy, and the underlying etiology of epilepsy, its relationship to drug exposure has not been thoroughly evaluated.

The pharmacokinetic (PK) profile of TPM after oral administration is well-documented.[9-15] TPM has many PK properties that are considered to be desirable. It is rapidly absorbed with peak plasma levels (C_{max}) observed 1-4 hours after administration, mean C_{max} and area under the concentration-time curve are linearly related to dose,[9,10] it is only 15% bound to plasma proteins,[16] and the major route of elimination is renal with 75-80% of the dose excreted unchanged in the urine.[15] Previous studies in healthy volunteers found TPM plasma concentration to have the largest influence on changing of verbal fluency scores and working memory tests after a single TPM dose of 100 mg; however, no quantitative assessment for the exposure-response relationship was provided.[2,17] The objective of this analysis was to develop a PK-PD approach to assess and quantify the effects of a low dose of TPM (50- 100 mg) given both orally and intravenously on generative verbal fluency as measured by the Controlled Oral Word Association test (COWA). In order to characterize the effects of TPM on COWA while excluding other confounders, we recruited adult healthy volunteers since patients with epilepsy are, by the nature of their disorder, prone to cognitive impairments including those related to verbal fluency tasks. A novel stable-labeled (SL) intravenous (IV) formulation of TPM developed by our group was administered and a sequential PK-PD modeling approach was utilized to characterize the PK and exposure-response relationship using the

following strategy: First, a PK model was established to describe the plasma concentration-time profile of TPM and to predict plasma concentrations at the exact time the COWA test was administered. Furthermore, the PK-PD relationship for TPM was characterized by relating the plasma concentration of TPM to the observed scores of COWA.

4.2 METHODS

4.2.1 Subjects

The subjects were healthy volunteers recruited from two centers: the University of Minnesota (UMN) and the University of Florida (UF). Eligible subjects were native English speakers, 18 to 65 years of age who were not taking medications known to interact with TPM or alter cognitive functions. Exclusion criteria included a history of intolerance to IV administration of medication; histories of significant cardiac, neurologic, psychiatric, oncologic, metabolic, renal, or hepatic diseases; alcohol abuse within the past 5 years; non-native speakers of English; diagnosis of a language impairment/disability; uncorrected low vision; a dominant left-hand; a positive pregnancy test; the use of any investigational drug or device in the 30 days prior to screening. Eligible subjects underwent a brief physical and neurological examination. Information about date of birth, race, ethnicity, sex, height, weight, and medical and surgical history was collected at the screening visit. The study protocols were approved by the UMN and UF's Institutional Review Boards and subjects provided written consents prior to enrollment.

4.2.2 Study Design

The PK-PD data were pooled together from three randomized cross-over studies. The pharmacodynamic (PD) assessment consisted of a neuropsychological battery containing tests of phonemic (COWA) and semantic fluency, as well as discourse-level verbal fluency and recall tasks. This test battery was administered to the subjects during all visits. Only the scores from the COWA will be presented here since only the COWA was modeled.

The first study was a 4-visit, bioequivalence study of IV and oral TPM. Subjects were administered the COWA during the two non-drug visits (visit 1: pretreatment and visit 4: posttreatment). The study design stipulated that two subjects receive a dose of 50 mg IV TPM, followed two weeks later by a 50 mg oral dose. If no serious adverse events occurred, the remaining subjects (n=10) were randomized to receive a single oral or IV dose of TPM (100 mg) on their second visit. The infusion dose was administered over 15 minutes. Blood samples were taken at 0, 0.083, 0.25, 0.5, 1, 2, 4, 6, 10, 12, 24, 48, 72, 96 and 120 hours after dose. During visit 2, COWA was administered at 0.25, 2.5, and 6 hours post dose. Following a 2-week washout period, subjects were crossed over to the alternative treatment (IV or oral TPM) on visit 3 during which the same protocol as visit 2 was repeated.

The second study (UF) was a 4-visit, placebo-controlled trial where pre and post-treatment measures of COWA were obtained on visits 1 and 4, respectively. On visits 2 and 3, subjects (n=11) were randomized to receive a single oral dose of TPM (100 mg) or placebo. COWA was administered once during a time window of 2-3 hours after dose. A single blood sample was collected after administration of the COWA test. In all cases, the actual times of the blood draw and the COWA test were recorded. Visits 2 and 3 were separated by a one week washout period. TPM was measured at all visits to ensure washout.

The third trial (UMN) was a three-way crossover study designed similar to study II with the addition of a third treatment period that allowed the randomization of subjects (n=9) to receive a single dose of lorazepam (2 mg). In that study, lorazepam (LZP) was chosen to investigate the mechanistic aspect of TPM effects on cognition by separating the effects of TPM from sedation. Data from the LZP arm were excluded from this analysis.

4.2.3 Controlled Oral Word Association Test (COWA)

Phonemic generative verbal fluency was evaluated using COWA. COWA requires the subject to generate words other than proper names or nouns beginning with a specific letter of the alphabet; three 60-second trials are obtained using three different letters, F-A-S or B-H-R. In this study, the examiners alternated between these sets of letters during

different visits in order to minimize the learning effects on repeated testing. The word counts generated per the three trials were summed as the COWA score. In this analysis, COWA will be considered for modeling the exposure-response relationship of TPM and the effects on phonemic generative fluency, while results from other neuropsychological tests will be reported elsewhere.

4.2.4 Intravenous Topiramate Formulation

A general description of the synthesis and formulation of the SL-TPM is reported in a previous publication.[18]

4.2.5 Determination of TPM and SL-TPM Concentrations

For quantification of both TPM and stable-labeled TPM, the LC/MS method with simultaneous determination of nine antiepileptic drugs was adapted from Subramanian et. al.[19] Topiramate-d_{12} was used as the internal standard. The limit of detection was 0.5 ng/mL, and the limit of quantification was 0.04 µg/mL. The precision for TPM and stable-labeled TPM ranged from 2-5% and 3-5%, respectively. The accuracy values of TPM were between 97.6 – 102.5% and 95.2-106% for stable-labeled TPM.

4.2.6 PK/PD Analyses

The pharmacokinetic and pharmacodynamic parameters were estimated using nonlinear mixed-effects modeling as implemented in NONMEM (version 7, ICON Development Solutions, Ellicot City, MD, U.S.A.), compiled using Intel® Visual Fortran Compiler XE (Version 12.0.2.154 Build 20110112, Santa Clara, CA, U.S.A.). The first-order conditional estimation (FOCE) and Laplace integral approximation methods with $\eta - \varepsilon$ interaction produced estimates of the structural parameters, as well as estimates of interindividual and residual unexplained variability (RUV) for the PK and PK/PD models, respectively. Model selection was based on the change in NONMEM objective function value (OFV; for nested models), Akaike information criterion (AIC; for non-nested models), and the visual inspection of improvements in the diagnostic plots (observed versus population and individual predicted concentrations and conditional

weighted residuals versus predicted concentration and time). For testing covariate models, a decrease in the OFV of at least 6.63 (χ^2, $p \leq 0.01$, df = 1) and 10.83 (χ^2, $p \leq 0.001$, df = 1) were used as a cutoff values for forward inclusion and backward elimination, respectively.

4.2.7 Population Pharmacokinetic Model

Both one and two compartment PK models with first order absorption and elimination were tested to describe the plasma concentration-time profiles of TPM and SL-TPM. The models were parameterized in terms of clearance (CL), volume of distribution (V_c), first-order absorption rate constant (K_a), oral bioavailability (F) and for the two compartment model, intercompartmental clearance (Q), and peripheral volume (V_p). The between subject variability was estimated using an exponential error model and expressed as coefficient of variation (CV). Both intravenous and oral TPM were modeled simultaneously. This enabled the estimation of the oral bioavailability (F) of TPM and the testing of separate residual error models for each formulation. Plots of post-hoc estimates of PK parameters from the base model versus covariates were visually inspected to evaluate the magnitude and direction of the covariate effects. A standard forward inclusion-backward elimination approach was adopted for developing the covariate model. Continuous covariates, such as age, were modeled through linear and nonlinear regression on clearance and V_c. In addition, an allometric relationship between PK parameters and actual body weight was considered where the allometric exponent for the volume of distribution was fixed to 1 while that of CL was estimated from the data. The effect of categorical covariates (sex and race) was examined through a multiplicative model in order to obtain the fractional change in the pharmacokinetic parameters. Qualification of the final PK model was conducted by means of visual predictive checks (VPC).

4.2.8 PK-PD Models

The PK-PD models related the plasma concentration (C_t) of TPM to the effects on COWA for both intravenous and oral treatments. Both discrete distribution models and

continuous approximation were explored for modeling COWA. When approximating COWA as a continuous outcome, two types of link functions were investigated:

1. A linear link function with the possibility of predicting negative COWA scores at high TPM concentration.

2. An exponential decline function which restricts the COWA predictions to positive values as follows:

$$COWA_{ij} = BL_i \times \exp\{-KE \times C_{ij}\} \qquad \text{equation (1)}$$

Where $COWA_{ij}$ is the jth COWA score for the ith individual, BL_i is the baseline COWA score for the ith individual with an exponential random effect, KE is the exponential decline constant for the effect of TPM concentration.

Both the Poisson and Negative Binomial distribution models were explored for modeling COWA under the discrete distribution assumption.[20] In these models, the mean outcome was linked to TPM plasma concentration through the exponential function described previously in equation (1), and the -2 logarithm of the likelihood option was utilized along with the Laplace integral approximation method in estimating the models parameters. The development of the PK-PD models was performed on the basis of stepwise inclusion of candidate explanatory variables. Covariate models included testing for the effect of age, sex, race, number of COWA tests administered (N_{COWA}), and the sequence of administering treatments in the crossover design. Eventually, the parameter estimates from both continuous and discrete distribution models were compared and the final PK-PD link model was qualified using VPC.

4.3 RESULTS

4.3.1 Subjects Characteristics

Data from 32 individuals recruited across the three studies were pooled for this analysis. Overall, subjects received either 50 mg (n=2) or 100 mg (n=30) of oral TPM. Of the 32 subjects, 12 were crossed over to receive an infusion dose of 50 mg (n=2) or 100 mg

(n=10) of SL-TPM, and 20 were crossed over to receive the placebo. Study III contributed a third treatment period during which subjects received a 2 mg dose of lorazepam; however, data from that period were excluded from the current analysis. The characteristics of the studied population and the composition of the data set are summarized in Table 4.1.

4.3.2 Pharmacokinetic Analysis

Final PK model parameter estimates and goodness of fit plots are presented in Table 4.2 and Figure 4.1, respectively. The final PK model was a two-compartment linear model with first-order absorption and elimination and an exponential model for interindividual variability of CL and V_c. Due to the presence of sparse data, estimation of the interindividual variability of Q, V_p, K_a and F resulted in large η shrinkage of over 80%; consequently the variances of the η for those parameters had to be fixed to zero. A separate proportional error model best described the RUV in TPM concentration for each formulation. During the forward inclusion, only actual body weight (ABW) and sex showed a significant influence on the V_c (ΔOFV= 12.1 and 7.5, respectively, $p<0.01$). In contrast, the inclusion of ABW on CL resulted in an insignificant drop in the OFV (ΔOFV= 2.3, $p>0.01$), however, the estimate of the allometric exponent for CL was 0.41 with a 95% CI (-0.16, 0.99) which included the theoretical value of 0.75. Therefore, this parameter was fixed to 0.75 in the final model. When testing for a race effect, groups other than Caucasians were collapsed into one category due to the small number of subjects in these groups and the difficulty of estimating a distinct parameter for each effect. Age, sex, race and TPM formulation had insignificant effects on CL (ΔOFV< 6.63, $p>0.01$).

A full model that scaled CL, Q, V_c, and V_p for a standard 70 kg body weight while accounting for sex effect on V_c was built. Backward elimination of sex resulted in an insignificant rise in the OFV (an increase of 2.1, $p>0.05$) indicating a possible collinearity between ABW and sex. Therefore, sex effect was dropped and ABW on CL, Q, V_c, and V_p was retained in the final model as follows:

$$CL(L/hr) = 1.21 \times \left(\frac{ABW}{70}\right)^{0.75} \qquad \text{equation (2)}$$

$$Q(L/hr) = 1.02 \times \left(\frac{ABW}{70}\right)^{0.75} \qquad \text{equation (3)}$$

$$V_c(L) = 59.3 \times \left(\frac{ABW}{70}\right) \qquad \text{equation (4)}$$

$$V_P(L) = 12.1 \times \left(\frac{ABW}{70}\right) \qquad \text{equation (5)}$$

4.3.3 PK-PD Models

The distribution of the COWA scores in the dataset is shown in Figure 4.2. The figure shows a mean observed COWA score of approximately 40 and that a normal distribution model can reasonably characterize the nature of the observed data. Despite the lower AIC value of the linear model (AIC 826.6) compared to the exponential decline model (AIC 829.9), the former simulated negative values for COWA at high TPM concentrations and was abandoned in favor of the exponential decline function for the model development. This function has shown a reasonable fit through the data as demonstrated in Figure 4.3. The model incorporated a between subject variability (BSV) for the baseline COWA (BL) modeled as an exponential η, however, it produced a huge η shrinkage (>90%) when BSV was included on the decline rate constant (KE). As a result, the variance of η on KE was fixed to zero. When exploring the COWA scores collected on drug-free conditions (pre and post-treatment baselines and placebo), a systematic increase was observed with increasing number of administered COWA test (N_{COWA}) as shown in Figure 4.4. N_{COWA} was incorporated into the model as a categorical covariate with the pretreatment COWA score set as a reference group and fractional changes due to N_{COWA} were estimated. The 95% CI for estimates of the effect of any $N_{COWA} < 4$ on BL crossed the null value of 1, while those for any $N_{COWA} \geq 4$ significantly departed from 1. Therefore, a fixed effect for $N_{COWA} \geq 4$ was estimated and significantly decreased the OFV (ΔOFV= 16.1; $p<0.0001$). Age, sex, race, and sequence of treatments had no

significant effect on both the baseline and the decline rate of COWA. A backward elimination was not performed since there was only one covariate effect per parameter included in the model.

Despite the potential advantage of the negative binomial model in accounting for the overdispersion above the mean COWA scores, the PS distribution was assumed in the model development. This is because the PS model accommodated the overdispersion above the mean once the N_{COWA} ($N_{COWA}< 4$ versus $N_{COWA} \geq 4$) was incorporated into the model (OVDP 0.0071). It is worth mentioning that both the discrete and continuous data distribution models have produced similar parameter estimates and were of comparable predictability for the observed COWA as shown in Table 4.3 and Figure 4.5, respectively. In addition, the continuous data distribution model fit had a considerably lower AIC than the Poisson model. Consequently, the traditional analysis for continuous data was sufficient for the COWA. The final model linked the decline in COWA to C_t through an exponential function and accounted for the effect of repeated tests of COWA ($N_{COWA} \geq 4$) on BL as follows:-

$$COWA_{ij} = \left[BL \times \theta^{N_{COWA} \geq 4} \times \exp(\eta_{BL}) \right] \times \exp\{-KE \times C_{ij}\} + \varepsilon_{ij}$$

Where $N_{COWA} \geq 4$ equals 0 if COWA is being repeated for less than 4 times or 1 otherwise and ε_{ij} is the independent normally distributed residual error with a mean zero and variance σ^2_{ε}.

4.3.4 Visual Predictive Check

The results of the predictive checks for the PK model of both IV stable-labeled and oral TPM are shown in Figure 4.6. The predictive check plot for the PD link model is shown in Figure 4.7. The visual inspection of these plots indicates that the final models were adequate in simulating both the overall trend and variability encountered in the PK-PD dataset.

4.4 DISCUSSION

To the best of our knowledge, this is the first study to quantify the change in generative phonemic fluency with respect to changing TPM concentration. We identified such changes to occur at a relatively low dose of TPM and a narrow range of observed TPM levels (0.05 to 3 mg/L). In addition, the study design allowed the examination of the practice effect of COWA. A significant improvement of the performance on COWA was demonstrated after the third time the test was administered on the non-drug sessions. Scores of COWA, however, declined exponentially with increasing TPM concentration with a rate constant of 0.157 L/mg. This means that the ratio of the COWA score to baseline COWA decreases by a factor of 0.85, on average, with each mg/L increase in TPM concentration. TPM at the average observed peak concentration (2 mg/L) reduced the COWA score over baseline by an average of 27%.

The PK of TPM was described by a 2-compartment model with first-order absorption and elimination processes. After oral dosing, TPM was found to be rapidly absorbed ($T_{1/2}$, absorption ~15 minutes) with no significant lag time. In addition, the estimate of the oral bioavailability of TPM (1.08) indicated that TPM is completely absorbed from the oral tablets. On the other hand, the distribution of TPM was calculated to be relatively slow as demonstrated by a distribution half life ($\alpha_{1/2}$) of 6.5 hours in this population. Previous studies in adults suggested that TPM PK following oral administration is described by a one-compartment model, but were mostly based on the analysis of sparse PK data.[13,15] Given the rapid absorption of TPM and the immediate effect on COWA scores observed in our study, it is possible that TPM undergoes a faster equilibration with the site of action than predicted by the calculated $\alpha_{1/2}$. Our study design included a total duration of infusion and time to first PK sample of approximately 20 minutes; thus, this rapid distribution phase could have been completed before our first PK sample was obtained. TPM CL of a typical individual (70 kg) was estimated at 1.22 L/hr which is consistent with the estimates of previous studies on healthy volunteers and patients with epilepsy.[15,21,22] Age, sex and race had no effect on the CL of TPM in healthy volunteers, although a previous study found TPM CL to increase with a patient's age.[15] The subjects

in our study were healthy, young adults, and had normal renal function. This may explain the lack of age and other covariates' effect on CL.

Of particular interest is the significant increase in COWA scores after the third time that the test was administered on non-drug sessions. On average, subjects generated 12% more words after the 3rd test compared to previous test sessions. A practice effect and reduced anxiety of the examinees on repeated testing could have contributed to this phenomenon. Despite this increase in the non-drug sessions, TPM still decreased the performance on the COWA test and the mean score of COWA per three trials declined exponentially with increasing TPM concentration. The decline rate constant was estimated to be 0.157 L/mg, which means that the ratio of COWA score to baseline COWA decreases by a factor of 0.85, on average, with each mg/L increase in TPM concentration. At the average peak concentration (C_{max} 2 mg/L) observed after a TPM dose of 100 mg, the model predicts a 27% reduction in the number of words generated on COWA (~31 words/3 trials). The effects on generative phonemic fluency as measured by COWA is expected to be mainly due to exposure to TPM since the study population included only healthy volunteers with no complications of seizures, drug interactions or varying etiology of epilepsy.

Our findings are in keeping with previous reports of the cognitive effects of TPM in healthy volunteers. At baseline, individuals generated an average of 43 words/3 trials which fell within the normal range for the adjusted-for-age, sex, and education COWA scores.[23] Studies on healthy volunteers of comparable age to those in our study found mean and median baseline COWA scores of 45 and 43 words generated per 3 trials, respectively.[3,24] In addition, these studies reported averages of reduction in the COWA scores of 36% and 42% after daily doses of 300 mg and 400 mg maintained for a mean of 3 weeks, respectively.[3,24] Short-term exposure to higher doses of TPM may thus worsen performance on COWA than were observed in our study. On the other hand, varying degrees of habituation to the cognitive adverse events may occur with prolonged therapy and result in milder cognitive side effects than were observed on acute exposure.[25,26] Lee et al. found a significant but mild decline only in verbal fluency and tests of attention (14% and 15%, respectively) after one year of exposure to low dose of TPM (50 to 100

mg/day) in patients with newly diagnosed epilepsy, well-controlled for seizures and with no EEG abnormalities.[4] Other cognitive tests administered in this study were not significantly influenced by TPM at the end of the one-year follow up. The authors concluded that verbal fluency and attention could be less habituated than other cognitive components by the long-term use of TPM.

The present study identified an exposure-response relationship of TPM and COWA scores at a narrow range of TPM levels (0.05 to 3 mg/L) in healthy volunteers. A direct translation of this relationship to epilepsy patients is ambiguous; however, we suppose that this exposure-response profile would apply to patients with migraine or obesity.[27] Migraine patients were found to have similar baseline cognitive performance to healthy controls, with a selective and persistent effect of TPM (50-100 mg) on verbal fluency scores after both the titration phase and 8 weeks of maintenance therapy.[5] On the other hand, conflicting results were reported for the cognitive effects of TPM in epilepsy patients. The study by Lee et al, revealed a significant interaction between TPM daily dose and the difference in scores of the backward digit span ($P<0.01$) and verbal fluency tests ($P<0.05$) before and after initiation of TPM.[4] On the contrary, a previous study of patients with intractable epilepsy who underwent withdrawal of TPM (50 to 650 mg/day) in preoperative settings found neither the dose nor the serum levels of TPM to be predictive of the cognitive side effects.[28] However, for those patients, differences in the etiology of epilepsy and brain pathology, polytherapy and the variable length of maintenance time on TPM could have confounded the relationship between TPM concentration and effect on cognition.

It is worth mentioning that the narrow range of administered doses and concentrations in our study were limitations to investigating the PK-PD relationship at higher exposures to TPM. It is possible that the COWA-C_{TPM} relationship asymptotes to a maximum effect at higher doses of TPM with increased exposures producing less than a proportional decrease in cognitive function. As we studied the cognitive effects of TPM in healthy volunteers with no underlying diseases or confounding factors, the findings from the current study may not be readily generalized to the broader epilepsy population. In addition, the single assessment of subjects after receiving placebo has limited the

characterization of a continuous time-COWA relationship. Further studies are needed to characterize the cognitive effects of TPM at higher doses and the relative contribution of placebo and learning of neuropsychological tests to the proposed TPM effect.

In conclusion, we have characterized the exposure-response relationship of TPM concentration and its effects on phonemic fluency in healthy volunteers given single, low doses of TPM (50-100 mg). The improved performance on COWA after being administered for 3 times is likely due to a significant practice effect on drug-free conditions. Scores of COWA declined exponentially with increasing TPM concentrations, and the model predicted the ratio of the COWA score to baseline COWA to decrease by a factor of 0.85, on average, with each mg/L increase in TPM concentration. Further studies are needed to characterize both the PK-PD and time-response relationship in epilepsy patients at a higher and wider range of doses than were utilized in our study. These models can be useful in predicting subpopulations of patients who would be more susceptible to impairment of COWA while providing a PK/PD evidence-based dose optimization of TPM in such patient populations.

Table 4.1. Summary of the Subject Characteristics and the Variables of the Dataset Relevant for the Model Development Across the Three Studies

	Study I	Study II	Study III	Total
Number of subjects	12	11	9	32
Number of PK observations				
IV	155	--	--	155
Oral	159	11	9	179
Number of PD observations				
Pre-treatment	9	11	9	29
IV	30	--	--	30
Oral	30	11	9	50
Placebo	--	11	9	20
Post-treatment	8	11	8	27
Weight (kg)	78.24±16.3 76.9 (58.3-112.3)	79.06±13.69 78.76 (59.78-111.22)	71.2±11.74 72.27 (54.73-92.27)	76.54±14.21 77.27 (54.73-112.30)
Age (years)	35±13.27 31.5 (19-55)	33.64±11.07 31 (20-50)	21.78±1.56 22 (20-24)	30.81±11.66 26.5 (19-55)
Sex Men/women	6/6	7/4	7/2	20/12
Race Caucasian/AA/other/Unknown	11/1/0/0	7/3/0/1	6/1/2/0	24/5/2/1

Values are count, mean±SD or median (range); IV, intravenous; AA, African American

Table 4.2. Parameter Estimates of the Final Pharmacokinetic Model

Parameter	Estimate	RSE (%)	% IIV	RSE (%)
CL (L/hr)	1.21	5.72	19.1	24.1
V_c (L)	59.3	7.03	23.2	33.4
Q (L)	1.02	43.6		
V_p (L)	12.1	10.6		
K_a (hr^{-1})	2.99	18.1		
F	1.08	2.54		
Residual error- oral TPM	0.039 CV%= 19.6	19.2		
Residual error- IV TPM	0.005 CV%= 7.2	11.8		

CL, clearance; V_c, central volume of distribution; Q, intercompartmental clearance; V_p, peripheral volume of distribution; K_a, the first-order rate constant of absorption; F, oral bioavailability of TPM; RSE, relative standard error [= (standard error ÷ estimate)*100]; IIV, inter-individual variability; CV, coefficient of variation.

Table 4.3. Parameter Estimates of the PK-PD Models.

	Analysis of COWA as continuous data		Poisson distribution for discrete data	
Parameter	Estimate	RSE%	Estimate	RSE%
BL (words/3 trials)	42.5	3.48	42.4	3.51
KE (L/mg)	0.157	16.4	0.163	16.7
$\theta^{N\_COWA\geq 4}$	1.12	2.38	1.13	2.35
%IIV of BL	17	27.9	17.6	25.7
σ_ε^2 (words/3 trials)	7.1	14		
AIC	829.99		1124.31	

BL, baseline score of COWA; KE, the exponential decline constant for the effect of TPM concentration; $\theta^{N\_COWA\geq 4}$ estimate of the fractional increase in BL when 4 or more tests of COWA are given, IIV; interindividual variability expressed as % coefficient of variation, σ_ε^2 variance of the residual error expressed in terms of standard deviation; AIC, aikaiki information criterion; RSE, relative standard error [= (standard error ÷ estimate)*100]

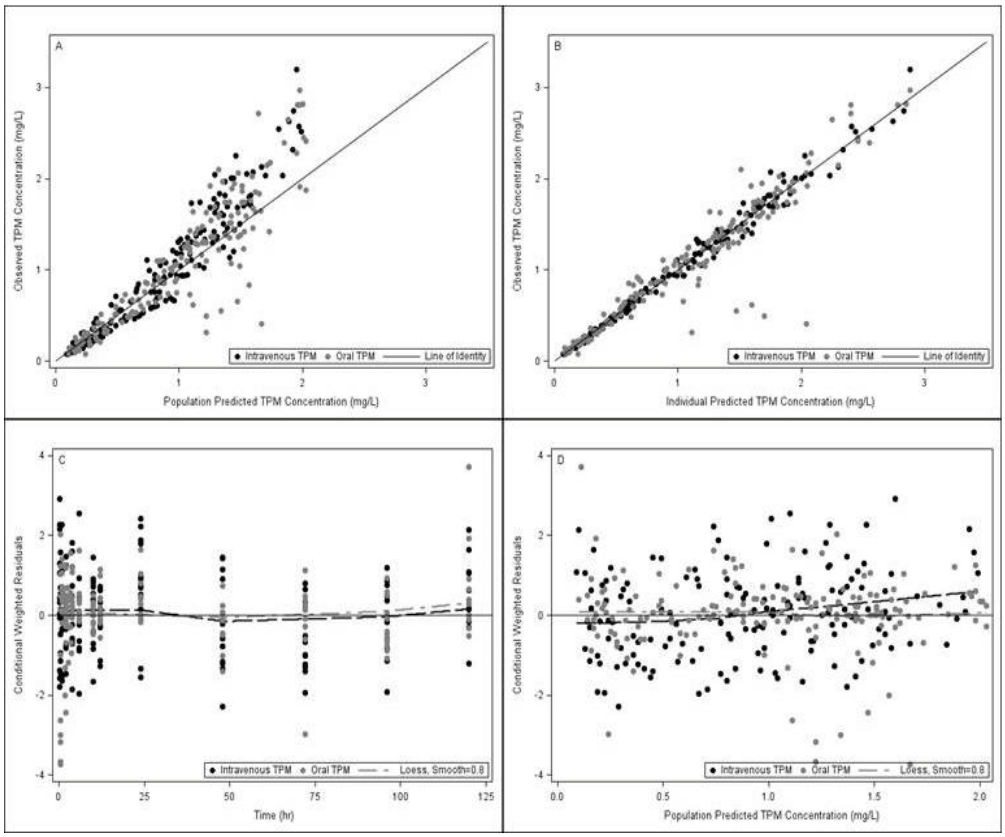

Figure 4.1. Goodness of fit plots from the final PK model. A) Identity plots of observed versus population predicted TPM concentration; B) Identity plot of observed versus individual predicted TPM concentration; C) Scatter plot of conditional weighted residuals (CWRES) versus time; D) Scatter plot of CWRES versus population predicted TPM concentration.

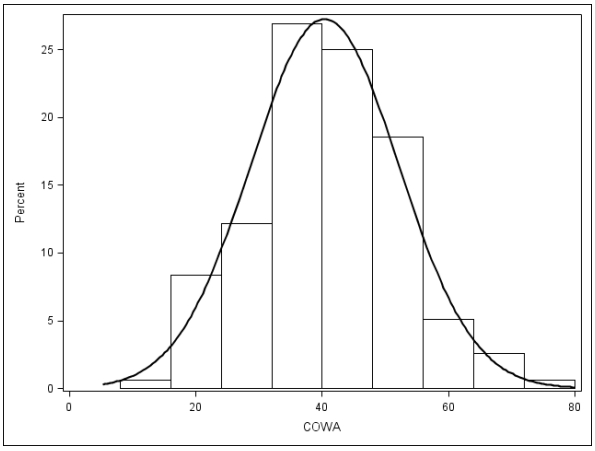

Figure 4.2. Histogram of the COWA scores in the dataset. Overlaid is a normal density.

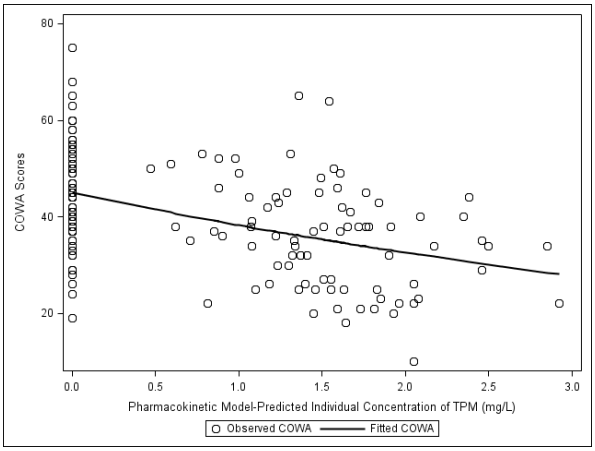

Figure 4.3. COWA versus PK model predicted individual TPM concentration. An exponential decline function is fitted.

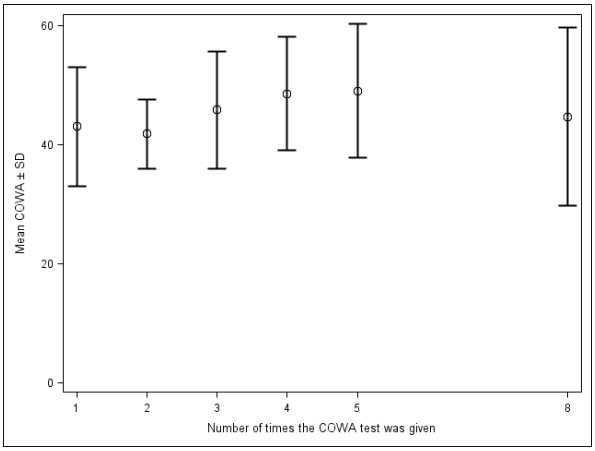

Figure 4.4. Mean scores of COWA±SD versus the number of times that the COWA test was administered.

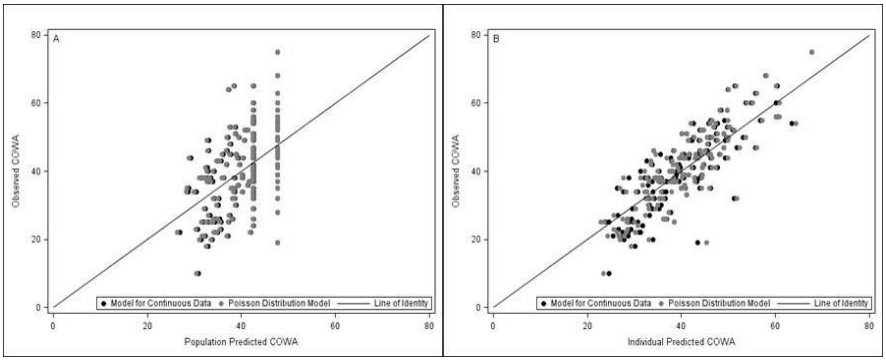

Figure 4.5. Goodness of fit plots from both analyses of continuous and discrete (Poisson) models. A) Identity plot of observed versus population predicted COWA. B) Identity plot of observed versus individual predicted COWA.

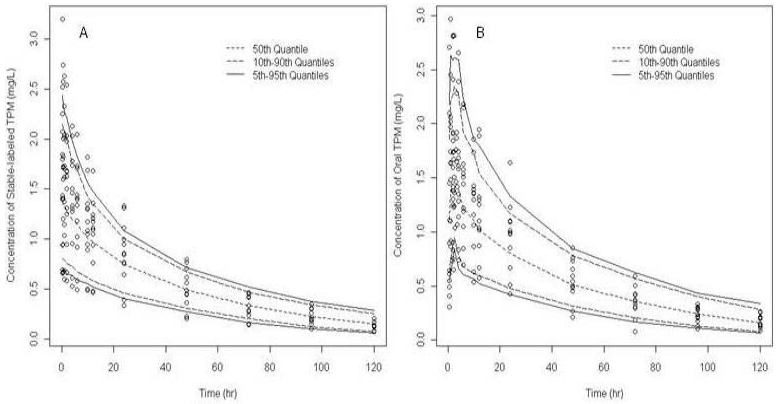

Figure 4.6. Visual predictive check plots of observed stable-labeled intravenous (A) and oral (B) TPM concentrations. Overlaid are quantiles of the simulated datasets from the PK model.

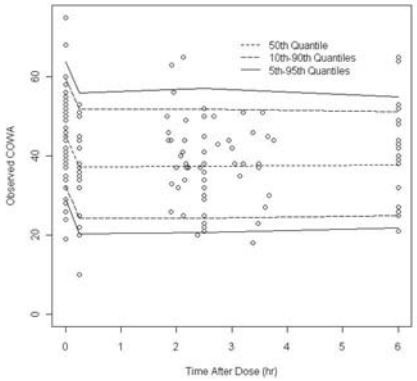

Figure 4.7. Visual predictive check plot of observed COWA with the overlaid quantiles of 1000 simulated datasets from the final PK-PD link model.

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CHAPTER V

Conclusions

The overall goal of this work was to characterize the interindividual variability in the pharmacokinetics (PK) and adverse cognitive effects of antiepileptic drugs (AEDs) in special populations. Three drugs were studied: Carbamazepine (CBZ), Gabapentin (GBP) and Topiramate (TPM). The PK of CBZ and GBP has been extensively studied in young adults and children; however, there is relatively sparse PK information about CBZ in the elderly compared to younger adults and absolutely no PK data about GBP in nursing home elderly patients. Optimal dosing of these AEDs in the elderly should be based on studies that are conducted in this patient population. This is because age-related changes in the PK can have a dramatic influence on the absorption, distribution, metabolism and elimination of AEDs. In addition, attention needs to be paid to the age-induced changes in pharmacodynamics (PD) as the elderly patients could be more sensitive to the effects of lower concentrations of AEDs with respect to both efficacy and adverse effects. As the elderly patients are reported to be more cognitively impaired than their community-dwelling peers and younger adults, understanding the mechanism and variability in AEDs-induced cognitive impairment is relevant to the optimal use of AEDs in this population.[1] We therefore attempted to characterize the exposure-response relationship of cognitive outcomes after low doses of TPM. The study was conducted in healthy volunteers so as to investigate the effects of exposure to TPM while excluding other confounders such as the underlying cause of epilepsy, polytherapy, and deteriorated cognitive functions due to age or other neurologic disorders.

We characterized, for the first time, the population PK of intravenous (IV) Stable-labeled (SL) CBZ under steady-state conditions in community-dwelling young adult and elderly populations. Distinct design features of the study are the use of a novel IV SL formulation as a partial replacement of CBZ oral dose coupled with a rich sampling schedule and the simultaneous modeling of both the unbound and total CBZ concentrations. This design enabled the rigorous estimation of the PK parameters under a clinically relevant setting without interruption of therapy. While community-dwelling elderly did not experience any age-related differences in clearance (CL), volume of distribution or protein binding compared to younger adults, we found a significant influence of race on the CL of CBZ. The study reported an average of 30% higher CBZ

CL in Caucasians compared to African Americans. This finding warrant further investigations before a dosing recommendation based on race is to be made. In addition, the inclusion of body weight has explained much of the interindividual variability in both the central and peripheral volumes of distributions (V). Other covariates such as sex, smoking, alcohol consumption or body size measurements had no discernable effect on CBZ CL. The binding of CBZ was shown to be constant (Fu ~0.25) over the range of studied unbound concentrations, however, this does not exclude the possibility of a nonlinear binding of CBZ at higher concentrations or frailer elderly population than in our study.

On the other hand, the PK characteristics of GBP in nursing home elderly were found to be markedly different from both community-dwelling older persons and younger adults. We found the CL of GBP in a nursing home resident with a normal kidney function (5.8 L/hr) to be slightly less than that of a community-dwelling elderly (8.5 L/hr).[2] Moreover, nursing home elderly had, on average, a smaller V for GBP (0.33 L/kg) compared to community-dwelling older patients with epilepsy (1.36 L/kg), healthy volunteers (0.6 L/kg) and younger adult patients with neuropathic pain (0.91 L/kg).[3-5] The implication of a smaller V is a shorter half-life ($T_{1/2}$) and elevated peak and trough plasma levels of GBP. We however found a diminished effect of decreased V on $T_{1/2}$ in nursing home elderly patients. Such a little effect was attributed, in part, to the lower renal clearance of GBP in nursing home (5.8 L/hr; % coefficient of variation 20) than healthier community-dwelling elderly patients (8.5 L/hr; % coefficient of variation 23.9) with normal renal function. While previous studies in community-dwelling elderly population concluded that dosage adjustment of GBP in the older patients should only be based on renal function, we came to a different finding in nursing home elderly. The absorption profile of GBP in the latter population reached the ID_{50} of saturation at a much lower dose (~486 mg) than in younger adults (~1100 mg). This may indicate a significant age-related effect on the gastric emptying rate and absorptive capacity of the small intestine. Our model-based simulation analysis found that dose fractionation; where a high dose (≥600 mg) of GBP will be divided to smaller doses given more often, would be warranted in this population as it maximizes the bioavailability, systemic exposure and efficacy with no expected increase in total dose or medication expenses. Caution is needed when

recommending such a complicated dosing schedule in elderly patients, as it can induce patient noncompliance and diminishes the potential gains from dose fractionation. Nonetheless, we believe that frequent dosing is unlikely to reduce compliance or complicate medication schedule in nursing home residents. Patients in the nursing home setting are routinely assisted by the facility's staff and caregivers for taking their medications, and often maintained on a long list of co-medications that are administered frequently during the day.[6] Future studies are needed to evaluate the relative importance of these factors in optimizing GBP dose for the elderly patients.

The determination of an optimal dose of AEDs necessitates the characterization of variability in response to adverse effects and the individual factors that would predict an increased susceptibility to these effects. As elderly patients are reported to be more cognitively impaired than their community-dwelling peers and younger adults, understanding the mechanism and variability in AED-induced cognitive impairment is relevant to dose optimization in this population.[1] Furthermore, large between subject variability in drug-induced adverse effects is observed with some patient populations experiencing severe enough effects to cause discontinuation of therapy.[7-12] Towards that end, we investigated the exposure-response relationship of TPM and its effects on phonemic generative fluency as measured by the Controlled Oral Word Association (COWA) test. Since patients with epilepsy are, by the very nature of their disorder, prone to cognitive impairments including those related to verbal fluency tasks, we recruited healthy volunteers for the initial study. This enabled us to characterize the effects of TPM on COWA while excluding other confounders. We found the performance on the word-level verbal fluency to decline in an exponential manner with increased TPM exposure. Such changes were identified at a narrow range of concentrations (0.05 – 3 mg/L) and low single doses (100 mg) of TPM. In addition, the PK/PD model quantified a significant practice effect estimated to be an average of 12% improvement in the COWA scores after the third time the test was administered on drug-free sessions. While accounting for the latter effect, TPM still decreased the performance on COWA, and the ratio of the COWA scores to baseline decreased by a factor of 0.85, on average, with each mg/L increase in TPM concentration. Whether this exposure-response relationship would translate to the broader population of patients with epilepsy is still unclear. Previous studies of the

cognitive effects of TPM in patients with epilepsy have reported conflicting results regarding the association between exposure and the response to cognitive impairment.[9,13] We expect this PK/PD relationship to also be observed in patients with migraine or obesity, as those patients are found to have similar baseline cognitive performance to healthy controls, and experience a selective and persistent effect of TPM on verbal fluency scores after both short and long-term maintenance therapy.[8] Our study was limited by the narrow range of administered TPM doses (50 to 100 mg) and the single assessment of subjects on drug-free sessions. As a result, characterization of both dose and time-response relationships of TPM-induced cognitive effects were not possible.

Future studies in healthy volunteers and adult patients with epilepsy will address the latter limitations and aim at developing predictive models of subpopulations of patients who would be at greater risk of cognitive impairment. The administration of a wider range of doses than used in our study is needed to investigate the dose-response relationship. The aims of these studies can further involve studying the regression of adverse cognitive effects towards baseline after withdrawal of TPM. Findings from these studies in both healthy volunteers and patients with epilepsy would be of clinical utility. For instance, it would inform the selection of an optimal time for TPM withdrawal before assessing patients with refractory epilepsy for cognitive performance in the preoperative setting.

Studies in patients with epilepsy should include patient samples with different racial mix and levels of education. These studies would also benefit from recruiting patients who are newly diagnosed with epilepsy and are prescribed TPM. In this case, both the acute and long-term effect of TPM can be characterized. In addition, the effect of varying degrees of habituation to the acute cognitive effects can be investigated. When contrasted with our findings in healthy volunteers, results from the latter studies would be beneficial in sorting out the effect of the disorder (e.g. epilepsy) from the effect of the AED (e.g. TPM). Eventually, these studies will contribute to the understanding of drug-induced cognitive impairment in the elderly population. The etiology of cognitive impairment is often multifactorial in these elderly patients. For instance, factors as the use of anticholinergic drugs, polypharmacy, age and disease-associated changes in brain

neurochemistry and drug effects can magnify the severity of the problem in this vulnerable population. Studies of healthy volunteers and adult patients with epilepsy can be used to generate hypotheses and explore the interaction between the older age-related factors and AEDs and epilepsy-induced cognitive effects in the elderly patients. On the long run, integrated evidences from studying cognitive effects of AEDs with predictive models of seizure control will provide a PK/PD-based dose optimization of AEDs in the elderly patients with epilepsy.

In conclusion, these studies characterized the interindividual variability in the pharmacokinetics (PK) and adverse cognitive effects of antiepileptic drugs (AEDs) in special populations of elderly patients. We found that the elderly population is a heterogeneous group, and that community-dwelling populations exhibit PK characteristics comparable to younger adults than to nursing home elderly residents. These findings indicate that extrapolation of results between different age groups within the elderly population may not be valid, especially for drugs that exhibit nonlinear PK properties. In addition to investigating the PK characteristics in the elderly patient population, studies in healthy volunteers provide the foundational work in investigation of the mechanistic aspects of adverse cognitive effects of TPM while excluding other confounders that are present in the patient populations. The population modeling approach was statistically powerful in analyzing data that were pooled from multicenter trials, studies of variable design and unbalanced data, and heterogeneous patient population.

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Appendix

Chapter II: NONMEM Code for Simultaneous Pharmacokinetic Modeling of Total and Unbound Carbamazepine Concentrations

```
;Model Desc: FINAL TOTAL AND UNBOUND CBZ MODEL
;Project Name: cbz
;Project ID: NO PROJECT DESCRIPTION

$PROB RUN# 059
$INPUT C ID CLNS TIME NTIM DV EVID TYPE AMT RATE AGE AGC1=DROP AGC2=DROP SEX RACE
ETH=DROP WT HT=DROP BSA=DROP LBM=DROP IBW=DROP DEI=DROP SEHI=DROP SMK=DROP
ETOH=DROP GPFT=DROP ATX=DROP NYPR=DROP NYPO=DROP ALB=DROP AAG=DROP
TOTP=DROP S002 S004=DROP S006 S007=DROP S013=DROP S016=DROP S026=DROP S027 S028
S032=DROP S033=DROP S039=DROP S045=DROP S047=DROP S052=DROP S055=DROP
S061=DROP S074=DROP S077=DROP S079=DROP S080=DROP S083 S084=DROP S085=DROP
S086=DROP S092=DROP S093 S097=DROP S103=DROP S105=DROP S109=DROP S113=DROP
S115=DROP S118=DROP

$DATA 103.CSV IGNORE=C
$SUBROUTINES ADVAN3 TRANS4

$PK
TVCL=THETA(1)
IF(RACE.EQ.4) TVCL=THETA(6)*THETA(1)
CL=TVCL*EXP(ETA(1))
TVV1=THETA(2)*(WT/70)
V1=TVV1*EXP(ETA(2))
TVQ=THETA(3)
Q=TVQ*EXP(ETA(3))
TVV2=THETA(4)*(WT/70)
V2=TVV2*EXP(ETA(4))
S1=V1

TVFU=THETA(5)
FU=TVFU*EXP(ETA(5))
SID=ID
TAD=TIME
AUC=AMT/CL
CAT1=TYPE

$ERROR
FCU=F
FCTOT=(F/FU)

IF(TYPE.EQ.0)THEN
Y = FCU*(1+ERR(1))*(1-TYPE)
ELSE
Y=FCTOT*(1+ERR(2))*TYPE+ERR(3)
ENDIF
```

```
IF(TYPE.EQ.0)THEN
IPRE=F
ELSE
IPRE=(F/FU)
ENDIF

IWRES=1

$THETA
(0, 10)          ;[RACE2, CL]
(0, 100)         ;[V1]
(0, 200)         ;[Q]
(0, 100)         ;[V2]
(0.01, 0.15)     ; [FU]
(0, 1)           ;[RACE4, CL]
$OMEGA
0.1              ;[P] omega(1,1)
0.1              ;[P] omega(2,2)
0.1              ;[P] omega(3,3)
0.1              ;[P] omega(4,4)
0.1              ;[P] omega(5,5)
$SIGMA
0.01             ;[P] sigma(1,1)
0.01             ;[P] sigma(2,2)
0.0001           ;[A] sigma(3,3)

$EST METHOD=1 INTERACTION PRINT=5 MAX=9999 SIG=3    MSFO=059.MSF
$COVARIANCE

$TABLE ID SID TIME TAD NTIM TYPE EVID CL Q V1 V2 FU SEX AGE WT DV RACE AUC WRES
CWRES IPRE PRED ONEHEADER NOPRINT FILE=059.tab
$TABLE ID CL V1 Q V2 FU NOPRINT ONEHEADER NOAPPEND FILE=059.patab
```

Chapter III: NONMEM Code for Population Pharmacokinetic Modeling of Gabapentin Concentrations in Nursing Home Elderly Patients

```
;Model Desc: FINAL GBP PK MODEL
;Project Name: gbp r01
;Project ID: NO PROJECT DESCRIPTION
;Project ID: NO PROJECT DESCRIPTION

$PROB RUN# 150
$INPUT C ID VISIT DATE=DROP TIME CTD NTIM DV AMT DOSE SS II MDV=DROP EVID=DROP CBZ
VPA OXC MOR ALMG ALC NAP HT WT NRHM SEX RACE ETH EDUC AGE EGFR BSA LBM  IBW BMI
BCOV BMC DCOV SRCR CRCL ACL TGFR ECL

$DATA 010.CSV IGNORE=C
$SUBROUTINES ADVAN2 TRANS2

$PK
TVCL=THETA(1)*(TGFR/69)**THETA(7)
CL=TVCL*EXP(ETA(1))
TVV=THETA(2)
V=TVV*EXP(ETA(2))
TVKA=THETA(3)
KA=TVKA
TVF1=1-((THETA(4)*DOSE**THETA(6))/(THETA(5)**THETA(6)+DOSE**THETA(6)))
F1=TVF1
S2=V

IF(AMT.GT.0) THEN
TDOS=TIME
TAD=0.0
ENDIF
IF(AMT.EQ.0) TAD=TIME-TDOS

DELCL= CL-TVCL
DELV= V-TVV

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

$THETA
(1, 2)          ;[CL]
(0, 10)         ;[V]
(0, 0.01)       ;[KA]
(0.1, 0.3)      ;[EMAX]
(100, 200)      ;[ED50]
(0.5, 2)        ;[HILL]
(0.1, 0.5)      ;[CRCL, CL]
```

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

$SIGMA
0.1             ;[P] sigma(1,1)

$EST METHOD=1 INTERACTION PRINT=5 MAX=9999 SIG=3    MSFO=150.MSF NOABORT
$COV

$TABLE ID TIME NTIM TAD TDOS VISIT DOSE AMT IPRE CWRES CBZ VPA OXC WT NRHM SEX
RACE ETH AGE EGFR DELCL DELV HT CL V KA F1 SRCR CRCL TGFR ETA1 ETA2 ONEHEADER
NOPRINT FILE=150.tab
$TABLE ID TIME CL V KA ONEHEADER NOPRINT FILE=PATAB150
$TABLE ID ONEHEADER NOPRINT FILE=COTAB150
$TABLE ID ONEHEADER NOPRINT FILE=CATAB150
$TABLE ID IPRE ONEHEADER NOPRINT FILE=SDTAB150
$TABLE ID CL V KA FIRSTONLY NOAPPEND NOPRINT FILE=150.par
$TABLE ID ETA1  FIRSTONLY NOAPPEND NOPRINT FILE=150.eta
```

Chapter IV

IV.A: NONMEM Code for Simultaneous Pharmacokinetic Modeling of Oral and Intravenous Topiramate Concentrations in Adult Healthy Volunteers

```
;Model Desc: FINALTWO COMPT MODEL ALL TPM DATA (IV&ORAL)
;Project Name: tpm_only_pk
;Project ID: NO PROJECT DESCRIPTION

$PROB RUN# 050
$INPUT C ID TIME NTIM DV AMT RATE MDV EVID DRUG CMT OCC WT AGE HT RACE BSA SEX
LBM IBW BMI

$DATA 106.CSV IGNORE=C
$SUBROUTINES ADVAN4 TRANS4

$PK
TVCL=THETA(1)*(WT/70)**0.75
CL=TVCL*EXP(ETA(1))
TVV2=THETA(2)*(WT/70)
V2=TVV2*EXP(ETA(2))
TVQ=THETA(3)*(WT/70)**0.75
Q=TVQ
TVV3=THETA(4)*(WT/70)
V3=TVV3
TVKA=THETA(5)
KA=TVKA
TVF1=THETA(6)
F1=TVF1
S2=V2

SID=ID
TAD=TIME
CAT1=DRUG

$ERROR
Y = F + F*(ERR(1))*DRUG+F*ERR(2)*(1-DRUG)
IPRE=F

$THETA
(0.1, 0.5)        ;[CL]
(1, 20)           ;[V2]
(0, 0.9)          ;[Q]
(0, 5)            ;[V3]
(1, 2)            ;[KA]
(0.01, 0.1)       ;[F]
$OMEGA
0.1               ;[P] omega(1,1)
```

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

$COV
$EST METHOD=1 INTERACTION PRINT=5 MAX=9999 SIG=3 MSFO=050.MSF

$TABLE ID TIME NTIM SID TAD DV AMT RATE MDV EVID CL V2 Q V3 KA F1 CAT1 DRUG IPRE PRED
WRES CWRES WT AGE HT RACE BSA SEX LBM IBW BMI ETA1 ETA2 ONEHEADER NOPRINT
FILE=050.tab
$TABLE ID CL V2 Q V3 KA FIRSTONLY NOAPPEND NOPRINT FILE=050.par
```

IV.B: NONMEM Code for Sequential Pharmacokinetic/Pharmacodynamic Modeling of Topiramate Effects on Phonemic Fluency Scores under the Continuous Approximation

```
;Model Desc: FINAL PK/PD MODEL FOR TPM/COWA UNDER CONTINUOUS APPROXIMATION
;Project Name: tpm_only_pk
;Project ID: NO PROJECT DESCRIPTION

$PROB RUN# 105
$INPUT C ID TIME NTIM DV NCOA AMT RATE CMT OCC MDV EVID SEQ TPM CLI V2I QI V3I KAI
F1I DRUG WT AGE HT RACE BSA SEX LBM IBW BMI

$DATA 022.CSV IGNORE=C
$SUBROUTINES ADVAN4 TRANS4

$PK
CL=CLI
V2=V2I
Q=QI
V3=V3I
KA=KAI
F1=F1I
S2=V2

IF(NCOA.EQ.0.OR.NCOA.EQ.1.OR.NCOA.EQ.2)THEN
TVBL=THETA(1)
ELSE
TVBL=THETA(1)*THETA(3)
ENDIF

BL=TVBL*EXP(ETA(1))
TVK=THETA(2)
K=TVK

SID=ID
TAD=TIME

$ERROR
CP=F

E=BL*EXP(-K*CP)
Y = E +ERR(1)
IPRE=E

$THETA
(20, 25)          ; [BL]
(0.01, 0.1)       ; [K]
(0.1, 0.3)        ; [NCOA2]
```

```
$OMEGA
0.1             ;[P] omega(1,1)
$SIGMA
0.01            ;[A] sigma(1,1)

$EST METHOD=1 INTERACTION PRINT=5 MAX=9999 SIG=3 MSFO=105.MSF
$COV

$TABLE ID TIME NTIM SID TAD DV CP AMT RATE MDV EVID CLI V2I QI V3I KAI F1I BL K DRUG IPRE
PRED WRES CWRES WT AGE HT RACE BSA SEX LBM IBW BMI ETA1 ONEHEADER NOPRINT
FILE=105.tab
$TABLE ID CLI V2I QI V3I KAI FIRSTONLY NOAPPEND NOPRINT FILE=105.par
```

IV.C: NONMEM Code for Sequential Pharmacokinetic/Pharmacodynamic Modeling of Topiramate Effects on Phonemic Fluency Scores under the Negative Binomial Distribution

```
;Model Desc: FINAL PK/PD MODEL FOR TPM/COWA UNDER THE NB FUNCTION
;Project Name: tpm_only_pk
;Project ID: NO PROJECT DESCRIPTION

$PROB RUN# 127
$INPUT C ID TIME NTIM DV NCOA AMT RATE CMT OCC MDV EVID SEQ TPM CLI V2I QI V3I KAI
F1I DRUG WT AGE HT RACE BSA SEX LBM IBW BMI

$DATA 022.CSV IGNORE=C
$SUBROUTINES ADVAN4 TRANS4

$PK
CL=CLI
V2=V2I
Q=QI
V3=V3I
KA=KAI
F1=F1I
S2=V2

$ERROR
TVOVDP=THETA(1)
OVDP=TVOVDP

IF(NCOA.EQ.0.OR.NCOA.EQ.1.OR.NCOA.EQ.2)THEN
TVBASE=THETA(2)
ELSE
TVBASE=THETA(2)*THETA(4)
ENDIF
BASE=TVBASE*EXP(ETA(1))
TVK=THETA(3)
K=TVK
CP=F

TVLAMB=TVBASE*EXP(-TVK*CP)
LAMB=BASE*EXP(-K*CP)

AGM1=DV+(1/OVDP)
AGM2=1/OVDP

LGAM1=LOG(SQRT(2*3.1415))+((AGM1)-0.5)*LOG((AGM1))-(AGM1)+LOG(1+1/(12*(AGM1)))
LGAM2=LOG(SQRT(2*3.1415))+((AGM2)-0.5)*LOG((AGM2))-(AGM2)+LOG(1+1/(12*(AGM2)))

LTRM1=(LOG(1/(1+OVDP*LAMB)))*(1/OVDP)
```

```
LTRM2=(LOG(LAMB/(LAMB+1/OVDP)))*(DV)

LDVFAC=0
IF(DV.GT.0) LDVFAC=LOG(SQRT(2*3.1415))+(DV+0.5)*LOG(DV)-DV+LOG(1+1/(12*DV))

LYY=LGAM1-LDVFAC-LGAM2+LTRM1+LTRM2
Y=-2*LYY

SID=ID
TAD=TIME
IPRE=LAMB

$THETA
(0.005, 0.009)   ; [OVDP]
(20, 25)         ; [BL]
(0.01, 0.1)      ; [K]
(0.1, 1)         ; [NCOA2]
$OMEGA
0.1              ;[P] omega(1,1)

$EST METHOD=1 LAPLACE -2LL PRINT=5 MAX=9999 SIG=3 MSFO=127.MSF
$COV

$TABLE ID TIME SID TAD DV AMT RATE MDV EVID CLI V2I QI V3I KAI F1I Y LAMB TVLAMB DRUG
IPRE PRED WRES CWRES WT AGE HT RACE BSA SEX LBM IBW BMI ETA1 ONEHEADER NOPRINT
FILE=127.tab
$TABLE ID CLI V2I QI V3I KAI FIRSTONLY NOAPPEND NOPRINT FILE=127.par
```

IV.D: NONMEM Code for Sequential Pharmacokinetic/Pharmacodynamic Modeling of Topiramate Effects on Phonemic Fluency Scores under the Poisson Distribution

```
;Model Desc: FINAL PK/PD MODEL FOR TPM/COWA UNDER THE PS FUNCTION
;Project Name: tpm_only_pk
;Project ID: NO PROJECT DESCRIPTION

$PROB RUN# 170
$INPUT C ID TIME NTIM DV NCOA AMT RATE CMT OCC MDV EVID SEQ TPM CLI V2I QI V3I KAI
F1I DRUG WT AGE HT RACE BSA SEX LBM IBW BMI

$DATA 022.CSV IGNORE=C
$SUBROUTINES ADVAN4 TRANS4

$PK
CL=CLI
V2=V2I
Q=QI
V3=V3I
KA=KAI
F1=F1I
S2=V2

$ERROR
IF(NCOA.EQ.0.OR.NCOA.EQ.1.OR.NCOA.EQ.2)THEN
TVBASE=THETA(1)
ELSE
TVBASE=THETA(1)*THETA(3)
ENDIF

BASE=TVBASE*EXP(ETA(1))
TVK=THETA(2)
K=TVK
CP=F

TVLAMB=TVBASE*EXP(-TVK*CP)
LAMB=BASE*EXP(-K*CP)

LDVFAC=0
IF(DV.GT.0) LDVFAC=LOG(SQRT(2*3.1415))+(DV+0.5)*LOG(DV)-DV+LOG(1+1/(12*DV))

TLYY=(DV*LOG(TVLAMB))-TVLAMB-LDVFAC

LYY=(DV*LOG(LAMB))-LAMB-LDVFAC

Y=-2*LYY
```

```
SID=ID
TAD=TIME

POIPROB=DEXP(TLYY)
IPRE=LAMB

$THETA
(20, 25)          ; [BL]
(0.01, 0.1)       ; [K]
(0.1, 0.9)        ; [NCOA2]
$OMEGA
0.1               ;[P] omega(1,1)

$EST METHOD=1 LAPLACE -2LL PRINT=5 MAX=9999 SIG=3 MSFO=170.MSF
$COV

$TABLE ID TIME SID TAD DV NCOA CP AMT RATE MDV EVID CLI V2I QI V3I KAI F1I Y POIPROB
LAMB TVLAMB DRUG IPRE PRED WRES CWRES WT AGE HT RACE BSA SEX LBM IBW BMI
ONEHEADER NOPRINT FILE=170.tab
$TABLE ID CLI V2I QI V3I KAI FIRSTONLY NOAPPEND NOPRINT FILE=170.par
```