THE ROLE OF COUNSELLING, MONITORING OF SERUM CARBAMAZEPINE CONCENTRATION, AND OF COMPLIANCE IN EPILEPSY CONTROL

BY

ROSALIE ANNE BRIDGENS

Submitted to the Department of Pharmacy
University of Limpopo (Medunsa Campus)
In partial fulfilment of the requirements
for the degree of
MSc (Med) Pharmacy

2012

TABLE OF CONTENTS

FOREWORD

As a pharmacist working in the Kalafong Hospital, I could not help becoming aware of the prominent role which compliance plays, particularly in epilepsy therapy. The potentially important roles that patient medication education and the monitoring of serum drug concentration might possibly play in the promotion of compliance, lay in my mind but evaded conceptive evaluation. This ultimately gave rise to the practical research work dealt with in this dissertation.

I am sincerely grateful to the many people who made it possible for my research to be brought to fruition. In particular, to Professor A. Gous, my mentor and Head of the Department of Pharmacy at the Medunsa Campus of the University of Limpopo, to Ms M. Leteka, Senior Lecturer, to Ms B. Pretorius, Librarian, to the laboratory staff and to the ever-helpful administrative staff of the Department, I owe much.

Grateful thanks also go to those at Kalafong whose valuable assistance enabled me to complete my research project, and in particular to the laboratory staff and the sisters who drew the blood samples.

I am also sincerely grateful to those who gave permission for me to carry out this work.

My sincere acknowledgement goes to Professor H.S. Schoeman and to Salome for their indispensable mentoring and valued assistance with the statistical analyses, the tables and the graphs.

Finally, thank you, Ms A. Dawes, for immaculate typing done so speedily in your private time.

Rosalie Bridgens
November 2012

ABSTRACT

THE ROLE OF COUNSELLING, MONITORING OF SERUM CARBAMAZEPINE CONCENTRATION, AND OF COMPLIANCE IN EPILEPSY CONTROL

Non-compliance with the patient's prescribed medication regimen has been identified in several publications as a major factor responsible for insufficient seizure control. Non-compliance is also held by some workers in this field to be closely interlinked with inadequate serum anti-epileptic drug concentration. The early identification of non-compliance may therefore play an important role in epilepsy therapy.

A study was undertaken at Kalafong Hospital to explore the efficacy of monitoring serum carbamazepine concentration in order to detect compliance or otherwise. Intrinsic in such study was exploration of the role played by counselling in the promotion of compliance.

Samples of blood were drawn from 78 outpatient volunteers at intervals as close to 28 days as possible, and the serum carbamazepine concentration of these samples was then determined by means of the TD_x FL_x System (ABBOTT).

Items such as conscientious attendance at the Kalafong epilepsy clinics ("visits"), serum carbamazepine concentration, patient's age, gender and weight, concomitant drug interactions, occurrence of epileptic seizures and dosage of Tegretol®CR were examined to ascertain whether they could be correlated with compliance and used as indicators thereof. It was, however, constantly borne in mind that these are not the only elements of compliance; other factors such as difficult fundamental behavioural changes, such as avoiding stress, may also play a part.

Conscientious attendance at Kalafong epilepsy clinics ("visits") was found to be a usable (albeit not strong) indicator of compliance. Serum carbamazepine concentration was used as another, with, however, reservations arising from the relationship between the patient's actual compliance on the one hand, and whether

the daily dosage was sub-therapeutic or excessive on the other. The statistical agreement between visits and these concentration values was, however, very poor (8.2%).

Using visits as an indicator, 66.7% of the participants were assessed as compliant. Using ‘compliant concentration’, only 25.6% were assessed as compliant.

The data acquired during the study was, unfortunately, too variable to warrant anything more than descriptive statistical treatment. To a large extent this was because the participants were out-patients, not in-patients over whom strict therapeutic control could be exercised.

Age, gender and patient’s weight were not significantly linked to compliance.

The correlation between expected and measured serum carbamazepine concentrations was not statistically significant ($p = 0.062$).

The Kalafong data in respect of seizures indicate that the relationship between seizures and compliance is not a simple one and that the occurrence or otherwise of break-through seizures should not be used as an indicator of compliance, as has indeed been done by other research workers.

Drug interaction was as expected in 20 of the 26 patients concerned, this agreement being statistically significant ($p = 0.0074$).

Improved compliance was the outcome expected from counselling but it was not possible to quantify the enhancement of compliance achieved, if any. Conventional verbal counselling, particularly when not done in the patient’s mother tongue and supported by interventions such as visual counselling material, may not be adequate.

CHAPTER 1. INTRODUCTION

The mere handing out of tablets to patients being treated for epilepsy cannot guarantee control of their seizures. Among other things, the degree to which these patients comply with their medication prescription can be of cardinal importance, as several decades of studies throughout the world have shown.

Cramer, Glassman & Rienzi (2002) investigated the relationship between poor medication compliance and seizures in patients undergoing treatment for epilepsy. Their study provided ample evidence that medication compliance is an important issue in the treatment of epilepsy. Other research workers concur with this view [Buck, Jacoby, Baker & Chadwick (1997); Cramer (2006); Lui, Yui, Yen, Chou & Lin (2003); Pellock, Smith, Cloyd, Uthman & Wilder (2004); Specht, Elsner, May, Schimichowski & Thorbecke (2003) and others].

The Kalafong Hospital records of some patients suffering from epilepsy do not testify to seizure control by dosage with combinations of carbamazepine and other antiepileptic drug (AED) therapy, in spite of seriatim increases in the dosages prescribed. Patients currently undergoing AED therapy at Kalafong are subjected to annual determinations of their serum carbamazepine concentrations, but this is an annual procedure and only assumptions with regard to the patient's daily compliance with his or her medication prescription can be made from this single test.

Regular, formal questioning of certain patients involved in this study and who were undergoing AED therapy at Kalafong Hospital has revealed that non-compliance with their medication prescriptions was relatively common amongst them. Some stop because they believe that they have been cured, others interrupt or stop their medication because they experience unpleasant effects, others forget to take their tablets several times a month and yet others did not fully understand the instructions repeated to them on each occasion of their visits to Kalafong Hospital to collect the next issue of their monthly AED;s.

The taking of the prescribed dosage is entirely under the control of these patients while they live at home, which most do. This suggests that compliance (or non-compliance) will be cardinal factors in successful treatment of their epilepsy, but other concomitant considerations also exist. These include the clinician's ability to utilise serum carbamazepine concentrations to determine or monitor the patient's degree of compliance, and also the promotion of an attitude in the patients that conscientious taking of their medication is important and in their own interest. Furthermore, the cost of monitoring compliance by way of more frequent determination of serum carbamazepine concentrations, pill counts, etc. needs to be considered in relation to the effectiveness of promotion of compliance through education and adequate motivation.

Studies of compliance in epilepsy control have been carried out in countries such as Germany (Specht *et al*. (2003), Singapore (Tan, Wilder Smith, Lim & Ong (2005)), Taiwan (Lui *et al*. (2003)), the United States of America (Cramer (2006)), and the United Kingdom (Patsalos & Perucca (2003a)) (see: Literature Review). It is however, important to recognise the cultural differences that exist between these countries and South Africa. The totally different African traditions and culture may possibly need different techniques, strategies and solutions, notwithstanding the similarities in the universal problem and ample evidence that medication compliance is an important issue in epilepsy therapy (Buck *et al*. (1997), Cramer (2006), Lui *et al*. (2003), Pellock *et al*. (2004)). Struwig & Stead (2003) remind us that research does not occur in a vacuum but is intimately bound to socio-historical, temporal and contextual factors.

It is therefore important to determine the role that counselling can play in ensuring medication compliance by epileptic patients at Kalafong, as well to determine whatever correlation there might be between their serum carbamazepine concentrations and their medication compliance. The significance of other compliance predictor variables such as, *inter alia*, age, weight, gender, and dose interval should also be determined. One aim of this study was to examine the efficacy of monitoring measured serum carbamazepine concentrations, and "compliant concentrations" also in the exploration of compliance by members of a

heterogeneous group of adult epileptic outpatients receiving monthly counselling and treated with one of three forms of the carbamazepine drug. The contribution made by counselling towards promoting compliance was also to be explored.

The objectives of the study were the following:

To determine individual measured serum carbamazepine concentrations at four consecutive 28-day intervals in a heterogeneous population of outpatients being treated for epilepsy, on which occasions they also receive counselling;
To ascertain whether such concentrations can be correlated with compliance or non-compliance, with due regard to relevant matters such as pill counts, fit chart records and predictor variables such as age, gender, concomitant drug interaction, race and dose intervals; and
To explore whether counselling makes for better compliance.

The achievement of these objectives may provide tools whereby effective motivation towards compliance can be achieved, as well as indications with regard to some of the factors which have militated against the implementation of an efficacious drug regimen.

This study may therefore be of value to those in the medical profession who are concerned with the treatment of epileptic outpatients who visit hospital clinics at monthly intervals for evaluation and to collect their prescribed medicine. If correlations are found, these may be helpful and possibly provide guidelines to those who are responsible for prescribing efficacious drug regimens. Where the actual response obtained to prescribed medication is either more or less than expected, the results of this study may also provide indications as to reasons therefore (e.g. drug interaction). Finally, this study may indicate whether compliance can be promoted by counselling.

CHAPTER 2. LITERATURE REVIEW

Some of the published work on compliance, the role of serum carbamazepine assay in epilepsy therapy, and the counselling of epileptic patients, done in countries such as Germany, Singapore, Taiwan, the United Kingdom and the United States of America, has been studied and will be considered in this literature review. It is however important to bear in mind that the African culture, environment and traditions may differ significantly from those elsewhere, and that the findings of the proposed research at Kalafong, being focused mainly on indigenous Africans, may therefore also differ from those of the international studies. Struwig & Stead (2003) note that there has been a gradual shift from focussing on issues from Western perspectives to examining research from African perspectives.

Buck, Jacoby, Baker & Chadwick (1997) mention that a comprehensive definition of compliance or non-compliance is not a straightforward matter. Aspects which they take into their definition include: not taking the correct dosage (too much or too little), failing to observe the correct interval of time between doses, not taking the medication for the duration specified, and taking other drugs not specified. To them, the strongest predictors of non-compliance are an attitude that it is not at all important to take their AEDs as prescribed, being a teenager, alternatively otherwise being aged under 60, and being on monotherapy. Just as the definition of compliance is problematic, so also can be its detection and measurement. Buck and her co-workers (1997) mention patients' reports, pill counts, blood tests, the outcomes, and the conclusions of those who tend them, as being relevant considerations.

The view of a number of research workers is that compliance is an important issue in epilepsy therapy (Buck *et al.* (1997); Cramer (2006); Lui, Yui, Yen, Chou & Lin (2003); Pellock, Smith, Cloyd, Uthman & Wilder (2004); Specht, Elsner, May, Schimchowski & Thorbecke (2003)). The degree of compliance or non-compliance mentioned in their publications varies, but the data presented in their publications should not be ignored. For example, Buck *et al.* (1997) found that 15% of their subjects missed taking a dose, but less than once a month. However, 9% missed

more frequently than once a month and 4% missed more frequently than once a week. McPhee & Pignone (2005) state that up to 50% of patients in an average practice may fail to achieve full compliance. Furthermore, they emphasize that, for non-English – speaking patients, healthcare delivery systems should endeavour to provide culturally and linguistically appropriate health services.

In an observational study, Doughty, Baker, Jacoby & Lavaud (2003) found that more than half their respondents missed taking their medication at least once a month, while 6% reported that they missed taking it at least once a week and 9% took more than the prescribed AEDs occasionally. As is to be expected, the studies of Whitehouse & Morris (1997) demonstrated a high rate of poor compliance among outpatients.

While there is general concurrence in the published literature that the degree of compliance will affect the occurrence of break-through seizures, several research workers also identify a number of other factors with compliance or non-compliance. Buck *et al.* (1997) found that patients under the age of 60, and teenagers in particular, tended more to non-compliance. Monotherapy or polytherapy was yet another factor, Buck *et al.* (1997) finding that this did not greatly influence the degree of compliance, while Doughty *et al.* (2003) noted increased compliance when their patients were moved from polytherapy to monotherapy. The overall findings of the last-mentioned workers suggest that switching from polytherapy with sodium valproate to monotherapy with sustained-release Depakine Chrono ® resulted, *inter alia*, in an improvement in compliance. Cramer, Glassman & Rienzi (2002) found that, while two or three doses per day did not unduly militate against compliance, the negative effect of more doses (and particularly if these were not given at convenient times) was marked. They added the caveat, however, that even reducing dosage to one dose per day will not guarantee perfect compliance.

Specht *et al.* (2003) regard non-compliance as a major cause of insufficient seizure control. Postictal serum concentrations (PISLS) were found by these workers to be

a simple and useful method for detecting or ruling out irregular intake patterns of patients' medication. In their study a method for differentiation of compliancy from non-compliancy was developed. Their standard practice was to determine serum concentrations of AED in patients on admission, after initiation of AED therapy, when seizures appear to be controlled, and when a previously prescribed AED is substantially altered.

The importance of convincing the patient that it is vital to take his or her medication strictly as prescribed has been mentioned by several research workers [Lui *et al*. (2003), Pellock *et al*. (2004) and others] and also Cramer (2006) who states that "teaching patients how to take their medicine probably is more important than explaining mechanisms of action". Conventional verbal education (counselling) of the patient is said to achieve good compliance. It may not, however, adequately cover drug-related issues and the consequent lack of AED knowledge results in decreased patient compliance, which is a serious hindrance to successful treatment Lui *et al.* (2003).

The Potentially Preventable Provocating Factors (PPPF) of Tan, Wilder-Smith, Lim & Ong (2005) were implicated in three-quarters of the seizure admissions of epileptic patients in Singapore. (These factors are: non-compliance, sub-therapeutic dosage, and deprivation of sleep). All of these factors are regarded by these workers as being amenable to education programmes.

Tomson, Dahl & Kimland (2010) reviewed aspects of routine therapeutic drug monitoring (TDM) as a guide to optimise the formulation of AED dosage regimens for patients with epilepsy. They found no evidence to indicate that routine TDM of serum was superior to adjustments of drug dose made on clinical grounds in respect of newly-diagnosed epilepsy patients treated with single drug carbamazepine. They did not, however, exclude the possibility that TDM of serum carbamazepine concentration could be useful in certain patients.

However, Eadie (1998) held the view that TDM methodology was currently already reasonably efficient and relatively satisfactory. He expected that future advances

in analytical methodology would make anti-epileptic drug monitoring in serum simpler, faster and cheaper than it was at that time. In his view, serum AED concentration monitoring is coming to be used in a more thoughtful and critical manner. Lack of adequate knowledge of matters such as the relationship between serum concentrations and anti-epileptic and toxic effects of the drugs, not only the newer but also the longer-established ones, in particular clinical situations, remains more important to him than deficiencies in analytical methodology in limiting the clinical usefulness of AED concentration. He maintains that a lack of adequate knowledge of matters such as the relationship between serum concentrations on the one hand and, on the other, anti-epileptic or toxic effects of both the older and newer anti-epileptic drugs (AED's, is important in assessing the clinical usefulness of serum AED concentration.

Their work on the detection or ruling out of irregular intake patterns of medication led Specht and his co-workers (2003) to conclude that the comparison of PISLS was a simple and useful technique. They found (postictal) that 44.3% of the breakthrough seizures studied were accompanied by a decrease of >50% in serum drug concentration in hospitalised patients.

Some of the individual dosage regimens of those patients used in the Kalafong study varied from monotherapy with carbamazepine, through polytherapy with a combination of two or more AEDs of which carbamazepine was one, to polytherapy with combinations of carbamazepine with drugs prescribed for the management of other disorders.

Interaction between carbamazepine and drugs prescribed for epilepsy and concomitant disorders other than epilepsy, has enjoyed the attention of the editors of a number of manuals, *inter alia* Beer & Berkow (1999); Di Piro, Talbert, Yee, Matzke, Wells & Posey (2002); Rossitor (2010); and Turner (2001).

In the first part of their review of clinically important drug interactions in epilepsy, Patsalos & Perucca (2003 a) summarised, *inter alia*, the main mechanisms of drug interactions and highlighted the more important interactions between AEDs.

Interactions between AEDs and drugs prescribed for the management of other disorders were discussed in part two of their review (Patsalos & Perucca 2003b).

For AEDs, pharmacokinetic interactions (ie those involving the absorption, distribution or elimination of the drug) are regarded by these authors as the most notable, but pharmacodynamic interactions (which take place at the site of action and result in a modification of pharmacological effects without any change in the drug concentrations in the serum) are also held to be important. (Patsalos & Perucca 2003a). Furthermore, several of the older generation AEDs such as carbamazepine are potent inducers of activity of certain hepatic enzymes involved in drug metabolism, leading, inter alia, to decreased serum concentration of the drug (Patsalos & Perucca 2003a). However, drugs other than AEDs can also affect the pharmacokinetics of AEDs, for example, the inhibition of carbamazepine metabolism by certain macrolide antibiotics, antifungals and isoniazid, resulting in appreciable increases in serum carbamazepine (Patsalos & Perucca 2003b).

In the Kalafong study, where the efficacy of monitoring serum carbamazepine concentrations for the determination of compliance was also in question, the potential interactions between AEDs and other drugs taken concomitantly, should therefore not be ignored.

Anti-epileptic drug therapy in patients with epilepsy is an ongoing process of seeking to balance disease control with somewhat unpleasant side effects (Lui *et al.* (2003). Drug-related adverse events are well known as a leading cause of the discontinuation by patients of their treatment regimens. According to Lui *et al.* (2003), medication education can measurably improve patient compliance and significantly reduce adverse drug-related events. However, in a study conducted by Lui and her co-workers (2003) it was also concluded that, despite achieving good compliance, conventional verbal information did not adequately cover all drug-related issues. Providing patient with written information “apparently” increased their knowledge of their medication and “probably” enhanced control of seizures (Lui *et al.* 2003).

The positive effect of education, presumably achieved by way of counselling, is supported by the work of Buck *et al.* (1997) who state that “further implementation of educational programmes for people with epilepsy would help to improve concentrations of compliance, thereby reducing unnecessary seizures.” A study by Peterson, McLean & Millingen (1984) who randomly allocated 53 hospital outpatients with epilepsy to either a control or an intervention group, and then subjected the intervention group to a combination of compliance-improving strategies, supports the contention of Buck *et al.* (1997). Both patient compliance and clinical control improved significantly in the patients of their intervention group.

CHAPTER 3: METHODOLOGY

INTRODUCTION

As mentioned earlier, one aim of this study was to examine the efficacy of monitoring measured serum carbamazepine concentration, and "compliant concentrations" also, in order to determine compliance or non-compliance. A further intention was to ascertain whether counselling promoted compliance with prescribed medication regimes.

To achieve these aims, the following objectives were set:

To determine the individual measured serum carbamazepine concentrations of the study population at 28-day intervals.
To ascertain whether such concentrations can serve as indicators of compliance and whether any correlations exist with predictor variables such as *inter alia*, age, gender, weight, and break-through seizures.
To explore whether counselling makes for better compliance.

The following forms of carbamazepine anti-epileptic drugs were used in this study, and in medically prescribed doses appropriate to each form:

Tegretol® Controlled Release 200mg
Tegretol® Controlled Release 400mg
Carbamazepine (generic) 200mg

STUDY POPULATION

Seventy-eight adult outpatients, which is more than the 60 planned for in the Study Protocol and all but one of whom were indigenous Africans who had been diagnosed as epileptic and were undergoing treatment for this condition at Kalafong Hospital, were recruited between February and May 2009 to participate in this study. Such patients had been undergoing therapy with one or another of the aforementioned drugs for a sufficiently long period (at least 3 months) to have

achieved a reasonably stable ('maintenance') concentration of serum carbamazepine. Inclusion criteria included the following:

The patient must be diagnosed as having epilepsy.
The patient must have been on treatment with one of the three forms of carbamazepine which will be used in this study, for at least the three months preceding its commencement. (Only one patient (ID 4) was on carbamazepine generic. Her results have therefore been included in the Tegretol®CR 200 mg group).
All available epilepsy patients being treated with Tegretol®CR or the 200 mg carbamezapine generic will be included, irrespective of whether they are undergoing monotherapy or multiple therapy.
Patient data which can be examined for a correlation between the carbamazepine taken by a patient and compliance, must be accessible.
Gender was not a consideration.
Patients younger than 16 years old were not included.

Being outpatients, compliance with their dosage regimen lay entirely in their hands, presumably making them ideal subjects for counselling.

Given the nature of this study, sample size was not a relevant consideration.

PATIENT PROCEDURE

In keeping with the relative procedures at Kalafong Hospital, the outpatients concerned were given at four consecutive 28-day intervals, sufficient tablets for 28 days' medication with the form of carbamazepine and other AED and non-AED medication which had been prescribed for them at that time.

They were required to collect these tablets personally from the Kalafong Pharmacy and to undergo a standard counselling on each such occasion, when a 5ml blood sample for the determination of their current serum carbamazepine concentration was also taken. The first such serum carbamazepine determination was used to

provide a baseline, with which the subsequent three determinations were compared.

Differences in the data pertaining to such serum carbamazepine concentrations were to be used appropriately to ascertain compliance and non-compliance. The resulting data are presented, *inter alia*, in Appendix Ci as “expected”, “measured” and “compliant concentrations”. In this regard it was borne in mind that Eadie (1998) had recognized that the timing of blood sampling for the determination of serum AED concentration recognised that the timing of taking blood samples for determination of serum AED concentration presented difficulties and mentioned trough concentration two to three hours before the next dose as the desired practice. This is an aspect of particular significance in the Kalafong study, where the participants were outpatients and the researcher consequently had no control over their medication or the interval between dose and blood sampling. To overcome this deficiency in the utilisation of measured serum carbamazepine concentration as a potential indicator, use was also made of “Compliant Concentrations” (Appendix Ci). The compliant concentration takes the time of last dose, blood specimen elapsed time after dose (position on the concentration-time graph) and possible influences of interactions with concomitant drugs into account and then correlates the result to the calculated expected concentration. A concentration is “compliant” if it correlates with the expected concentration even if it was outside the therapeutic range. For the level to be within the therapeutic range does not necessarily mean that the patient is compliant in taking carbamazepine regularly.

Pill counts (ie of unused pills) were to be done and recorded on every occasion when a new issue of medication was made in order to correlate with serum carbamazepine concentrations.

A record of epileptic seizures occurring during the trial would be compiled in respect of each patient. Seizures were recorded on the standard Kalafong Fit Charts, an example of which is at Appendix B to this Dissertation. In so far as

terminology is concerned, in this Dissertation the words *seizures* and *fits* have been used interchangeably as synonyms.

DATA COLLECTED

A comprehensive record of data collected during this study was compiled. This was done by the researcher who extracted the relevant data from the patients' files which are routinely maintained by the clinic personnel. Appendix A comprises a document presenting essential information in respect of each patient. In this regard, the Kalafong documents requesting TDM also place on record items such as age, gender, mass, race etc. some of which may influence the outcomes of the study.

Variables e.g. gender, age, mass, race, concomitant drug interactions, education status etc. are mandatory items which should be recorded in the procedure for TDM from information contained in the patient's file. These records were available to the researcher but were unfortunately not always complete and it was not possible to obtain the missing data. Consequently such deficiencies had to be recorded as "missing values". It had been intended to analyse the relevant data statistically in order to determine whether these factors influenced the outcome of the study in any way.

Blood samples were taken by way of Red-top vacutainers by appropriately qualified clinic personnel (e.g. nursing sisters or doctors) on the days on which the new supply of medication was issued. Standard procedures of the Kalafong Hospital's SANA-accredited Laboratory were followed where relevant, including the storage of each sample at temperatures within the range 2°C to 8°C until it could be centrifuged and the serum separated from the blood cells and frozen. Serum carbamazepine concentrations were determined by the appropriate SANA-accredited laboratories at the Medunsa Campus of the University of Limpopo. These data will be found in the data spreadsheets at Appendix C.

Pharmacokinetic considerations with regard to time of sampling (i.e. collection of blood samples) were observed, as far as was possible. However, as the time

elapsed between the patient's last dose of Tegretol®CR and the blood sampling, varied from sample to sample and patient to patient, data *inter alia* taking cognisance of this and of interactions with concomitant drugs, if any, were also included in Appendix Ci as "compliant concentrations". These "compliant concentration" data were obtained from a computer program which took such variability into account.

The professionally accepted procedures for calibration of equipment and for the determination of serum carbamazepine concentrations, as followed by the SANA-accredited laboratory in the Department Pharmacology and Therapeutics at Medunsa Campus were followed and these were in keeping with the drug regimen prescribed for the patient. In brief, the TDxFLx System (ABBOTT) used by this laboratory utilises the technique of fluorescence polarisation immunoassay. The observed fluorescence of a fluorescein labelled drug tracer is inversely (indirectly) proportional to the drug concentration. The exact concentration of the drug in a sample is determined by extrapolation from a calibration curve stored in the Analyser memory. A more complete description of the procedure concerned is at Appendix D.

EXPECTED SERUM CARBAMAZEPINE CONCENTRATION

The expected serum carbamazepine concentrations were calculated using the following formula:

$$C = \frac{D \times F \times S}{Cl \times W \times 24}$$

Where C = expected serum carbamazepine concentration expressed in µg/ml

D= daily dose of Tegretol®CR 200mg or 400mg, or carbamazepine (generic) 200 mg

F= bioavailability factor with the fixed value of 0.7 for Tegretol®CR

S= salt factor with the fixed value of 1.0 for Tegretol®CR

Cl= clearance: for Tegretol®CR taken as being 0.07 ml/minute/kg patient weight

W= patient's weight

24= 24-hour day

Monitoring of carbamazepine concentrations in each 5ml blood sample was done to assist evaluation of compliance and of differences in serum drug concentrations.

The initial serum carbamazepine concentration for a particular patient was taken as the benchmark value for that patient.

The following will be regarded as the optimum range of serum carbamazepine concentrations: 4µg/ml to 12µg/ml as per University of Limpopo (Medunsa Campus) standards.

COMPLIANT CONCENTRATION

However a measured concentration was considered "compliant" if it correlates with the "expected concentration" even if it itself was outside the therapeutic range. Being within the therapeutic range does not necessarily mean that the patient is compliant in taking carbamazepine regularly. The calculated expected

concentration, which is an average concentration for that dosing interval was compared with the measures concentration. The time the specimen was taken in relation to the last dose also was interpreted according to the concentration-time graph to determine whether the patient was compliant. For example a patient could be determined to be non-compliant if the measures concentration did not correspond with the concentration expected according to the concentration-time graph even if there is minimal difference between the measured and expected concentration.

SEARCH FOR INDICATORS OF COMPLIANCE OR NON-COMPLIANCE

For reasons which will be dealt with in detail in *Chapter 5: Discussion*, the following factors will be tentatively explored in this study to initiate a search for indicators of compliance or otherwise:

a measured serum carbamazepine concentration within the range 4µg/ml to 12µg/ml, and correlating with the respective expected concentration value;

regular visits by the patient to the Kalafong Hospital Clinic with, however, due cognisance of the logistic difficulties confronting the patient. Therefore, because of the logistic and financial constraints affecting the out-patient, any visit within a period of two days before to two days after due date was perforce regarded by the researcher as indicating compliance.

This is in deference to the views of other workers (Buck *et al*. (1997); Eadie (1998); Specht *et al*. (2003)) with regard to the role that these indicators may play. As the validity of their use as such indicators is, however, open to question, this will be only a first, exploratory step in this regard. However, as mentioned in Chapter 5, this does not imply that these two are regarded as the only elements impacting on compliance.

STATISTICAL ANALYSIS OF DATA

Categorical variables (gender, fits and compliance) were summarised by, *inter alia*, frequency counts and percentage calculations.

Continuous variables (age, weight, and daily dose of Tegretol® CR, serum carbamazepine concentration) were summarised by, *inter alia*, sample size, mean values, median values, standard deviation and minimum and maximum values. The reason for the indication of “missing values” has been mentioned previously.

Drug interaction was summarised descriptively with due interpretation of the implications of these in respect of compliance.

All statistical analysis was performed on SAS, Release 9.2, running under Microsoft Windows for a personal computer.

P values $\leq$ 0.05 were considered to be statistically significant.

COUNSELLING

Counselling started for each patient with an in-depth explanation and discussion of the *Guidelines for Counselling and Patient Information Leaflet and Statement of Informed Consent for Participation in a Research Project* (see Appendix E). The purpose and methodology of the Kalafong study were also explained, as were the rights of the participant, confidentiality and what was expected from the patient.

The formal counselling of each patient was individually repeated by the responsible research pharmacist on each occasion when that patient reported to the Kalafong Hospital Clinic to collect the following month’s prescribed supply of medication.

On each occasion stress was laid on the necessity for conscientious taking of the tablets in the correct dosage and at the correct intervals. Also stressed was the purpose of each tablet, what to do when a dose was missed, and visual guidance was provided by physically setting out examples of the respective tablets in their prescribed doses. If linguistic problems arose, the researcher made every effort to obtain assistance from the limited pharmacy staff. Unfortunately such assistance was not always available.

The patient was quizzed on doses missed, the occurrence of fits, side effects, and unused tablets, and appropriate records were compiled.

After due consultation with the medical doctors, nursing staff and pharmacists concerned, a standard format for the counselling “treatment” was compiled. Guidelines for such counselling are at Appendix E. However, as the study got underway it became evident that, in the planning of the counselling the research worker had been in error to assume that such counselling would markedly enhance compliance. In the original planning it had been confidently expected that the improved compliance would be clearly reflected in whatever indicators were used, and that the effect of counselling could be assessed thereby.

ETHICAL FORMALITIES

Strict confidentiality of information, and of results pertaining to a patient, as well as anonymity of the patient has been observed for example, *inter alia* by the allocation of personal numbers to patients.

All relevant mandatory and customary ethical formalities were observed. These included *inter alia,* prior consent of the patient (an example of a formal document of consent is at Appendix E.)

formal approval of the protocol was obtained from the University of Limpopo Medunsa Campus Research Ethics Committee, and
approval from the Chief Executive Officer of Kalafong Hospital was given for such study to be conducted by me at Kalafong Hospital.

CHAPTER 4: RESULTS

INTRODUCTION

A group of 78 outpatients, composed of 77 indigenous Africans and one Caucasian, all of whom were attending clinics at the Kalafong Hospital, was used for this study. They participated voluntarily, and strict confidentiality and anonymity of patient were observed. Being outpatients, their compliance with their dosage regimen lay entirely in their own hands, potentially making them ideal subjects for counselling in respect of compliance. They had all been diagnosed as epileptic and had been undergoing treatment for at least three months with carbamazepine.

CONSTRAINTS ENCOUNTERED DURING THE KALAFONG STUDY

Shortly after the study was launched, several unforeseen complications emerged. Being outpatients, the participants in this study were not under continuous supervision and care. The taking of their medication lay entirely in their own hands for the entire duration of the study, during which they kept no records for use at the de-brief when they collected their new supply of medicines and received further counselling. Peterson, McLean & Milligen (1984) mention similar constraints with the outpatients recruited for their studies. Whitehouse & Morris (1997) also mention a low level of compliance amongst outpatients.

Of necessity, the Kalafong patients had to arrange and finance their travel to and from the hospital, which is not served by convenient transport. Amongst other things, the irregular availability of such taxis as were at their disposal made their arrival at stipulated times unlikely.

Another unforeseen factor was that patients sometimes sent their children to collect the next issue of their AED.

A chronic shortage of staff existed at Kalafong Hospital and trained staff were not always immediately available when needed during clinic hours. Consequent delays in consultations and in the taking of blood samples were inevitable and were often exacerbated by unpunctual patients.

The time elapsing between the last dose of Tegretol®CR taken by the patient and the blood sampling; was dictated by their personal circumstances and was inevitably variable. It also varied from patient to patient. However, in the compilation of the "compliant concentrations" account was duly taken of this.

Counts of unused tablets ("Pill Counts") had to be abandoned as an indication of regular taking of medication, as only two patients ever reported with unused pills from the previous issue.

The problems mentioned here introduced so much variability into the data collected that refined statistical analysis such as logarithmic regression could not be employed, and recourse had to be taken to descriptive statistics only.

The results of this study are presented in Tables 1 to 15. The basic data from which these tables have been derived are presented in the spreadsheets at Appendix Ci and Cii.

Note

In this dissertation the following statistical convention has been followed:

(15 ; 30] i.e. greater (not equal to) than 15, up to and including 30.
(30 ; 45] i.e. greater (not equal to) than 30, up to and including 45.

Note: use of "("and of"]" brackets

TABLES 1 and 2 - Gender of patients

The statistics with regard to the gender of the patients used in this study are summarized in Tables 1 and 2. From Table 1 it will be seen that almost two-thirds (64.1%) of the patients were male.

Table 1: Gender ratio

Gender	Number (%) of patients
Male	50 (64.1%)
Female	28 (35.9%)
Total	**78 (100%)**

Table 2: Effect of gender on compliance

		Compliance Indicated by Visits			Compliance Indicated by measured serum concentration		
		Males	Females	Total	Males	Females	Total
Yes	**Number**	33	19	52	29	12	41
	%	52.4	30.2	82.5	39.7	16.4	56.2
No	**Number**	10	1	11	18	14	32
	%	15.9	1.6	17.5	24.7	19.3	43.8
	Total	43	20	63	47	26	73

Visits: The compliance for 15 (males = 7; females = 8) patients could not be determined as either yes or no.

Serum concentration: the compliance for 5 (males = 3; females = 2) patients could not be determined as either yes or no.

Patients were taken as compliant by visit or serum concentration if the number of compliance with criteria were more that 50%. The complete dataset is presented as Appendices Ci and Cii.

The differences in Table 2 are not significant, notwithstanding the indication that females were more compliant than males when their compliance was indicated by *visits*. The reverse was the case when compliance was indicated by serum carbamazepine concentrations.

TABLES 3 and 4 – Ages of patients

Taken collectively, the ages of the patients ranged from 16 to 68 years. The individual ages of these patients were grouped into appropriate incremental 15-

year class intervals (Table 3). The majority of the patients (93.3%) were younger than 60 years of age, 60% of these being 45 years old or younger. The mean age of the group used for the study was 42.57 years, with a median group age of 43 years.

Table 3: Patient Age

Age, years	**Number (%)**	**Cumulative (%)**
(15 ; 30]	17 (22.7)	17 (22.7)
(30 ; 45]	28 (37.3)	45 (60.0)
(45 ; 60]	25 (33.3)	70 (93.3)
> 60	5 (6.7)	75 (100)
Total	**75 (100)***	
N	75	
Mean	42.57	
Std deviation	13.16	
Median	43.00	
Minimum / Maximum	16 / 68	

*** 3 missing values**

Table 4: Effect of Patient's age on compliance

	Compliance Indicated by visits				**Compliance Indicated by measured serum concentration**			
Age class (years)	**Number (%) n=75**				**Number (%) n= 75**			
	Y	**N**	**U**	**Total**	**Y**	**N**	**U**	**Total**
(15 ; 30]	9 (12.0)	2 (2.7)	6 (8.0)	**17 (22.7)**	13 (17.3)	4 (5.3)		**17 (22.7)**
(30 ; 45]	17 (22.7)	6 (8)	5 (6.7)	**28 (37.3)**	20 (26.7)	6 (8.0)	2 (2.7)	**28 (37.3)**
(45 ; 60]	20 (26.7)	2 (2.7)	3 (4.0)	**25 (33.3)**	7 (9.3)	15 (20.0)	3 (4.0)	**25 (33.3)**
> 60	4 (5.3)	1 (1.3)		**5 (6.7)**	1 (1.3)	4 (5.3)		**5 (6.7)**
Total	**50 (66.7)**	**11 (14.7)**	**14 (18.7)**	**75 (100)**	**41 (54.7)**	**29 (38.7)**	**5 (6.7)**	**75 (100)**
P values	P = > 0.1				P = > 0.1			

Y = Yes N = No U = Undetermined ie patient presents with identical numbers of Y and N, thereby preventing unequivocal classification as either Y or N.

The age of three patients were not recorded.

For both modes of assessment (visits and measured serum carbamazepine concentrations) no association was found between compliance and age as shown by the p values in the table.

TABLES 5 and 6 – Weights of patients

Taken collectively, the body-weights of the patients ranged from 44kg to 117kg. The individual weights of these patients were grouped into appropriate incremental 20-kg weight class intervals (Tables 5 and 6). Fifty per cent of the patients fell into the weight group 60kg to 80kg. The mean weight of the group of 76 patients was 71.86kg, with the median weight being 70kg.

Table 5: Patients' Weight

Weight, kg	**Number (%)**	**Cumulative (%)**
(40 ; 60]	20 (26.3)	20 (26.3)
(60 ; 80]	38 (50.0)	58 (76.3)
(80 ; 100]	15 (19.7)	73 (96.1)
(100 ; 120]	3 (4.0)	76 (100)
Total	**76 (100) ***	
N	76	
Mean	71.86	
Std deviation	14.83	
Median	70.00	
Minimum / Maximum	44 / 117	

***2 missing values**

Table 6: Effect of patient's weight on compliance

Weight class (kg)	Compliance Indicated by visits				Compliance Indicated by measured serum concentration			
	Number (%)				Number (%)			
	Y	N	U	Total	Y	N	U	Total
(40 ; 60]	13 (17.1)	4 (5.3)	3 (3.9)	**20 (26.3)**	10 (13.2)	9 (11.8)	1 (1.3)	**20 (26.3)**
(60 ; 80]	26 (34.2)	5 (6.6)	7 (9.2)	**38 (50.0)**	20 (26.3)	15 (19.7)	3 (3.9)	**38 (50.0)**
(80 ; 100]	9 (11.8)	1 (1.3)	5 (6.6)	**15 (19.7)**	9 (11.8)	5 (6.6)	1 (1.3)	**15 (19.7)**
(100 ; 120]	2 2.6()	1 (1.3)		**3 (3.9)**	1 (1.3)	2 (2.6)		**3 (3.9)**
Total	**50 (65.8)**	**11 (19.7)**	**15 (19.7)**	**76 (100)**	**40 (52.6)**	**31 (40.8)**	**5 (6.6)**	**76 (100)**
p values	p = > 0.1				p = >0.1			
	2 missing values				2 missing values			

Y = yes N = no U = undetermined i.e. patient presents with identical numbers of Y and N, thereby preventing final classification to either Y or N.

For both modes of assessment (visits and serum carbamazepine concentrations) no association was found between compliance and weight as shown by the p values in the table. If conscientious visiting of the clinic at Kalafong Hospital and the accepted serum carbamazepine concentration were regarded as valid indicators of compliance, the data of Table 6 (Effect of Patient's weight on compliance) do not indicate any affinity between patient's weight and compliance.

DOSAGE

Table 7: Mean daily dose of Tegretol® CR

Daily dose, mg	Number of patients(%)	Cumulative (%)
[200 ; 400]	17 (25.0)	17 (25.0)
(400 ; 800]	30 (44.1)	47 (69.1)
(800 ; 1200]	14 (20.6)	61 (89.7)
(1200 ; 1600]	7 (10.3)	68 (100)
Total	**68 (100)***	
N	68	
Minimum / Maximum	200 / 1600	

***10 missing values**

The daily dose of Tegretol® CR or carbamazepine (generic) prescribed for patients in the study group varied from 200mg to 1600mg (Table 7). The largest sub-group comprised 30 patients (44.1%) and each of these patients received a daily dose of between 400mg and 800mg. Twenty-five patients were also taking other AEDs as well, while yet others were also undergoing treatment for illnesses other than epilepsy and were taking the appropriate concomitant medication. Data in respect of the relevant concomitant AED medication is presented in Table 12.

FITS

Table 8: Patients' Fits

Occurrence of Fits	Number of Patients (%)
No	52 (66.7)
Yes	26 (33.3)

In spite of their prescribed regimens of AED therapy, 33.3% (26 patients) of the study group reported that they had had at least one breakthrough fit during the period of the study, while 52 patients (66.7%) did not report having had any seizures during that time (Table 8).

The group of 26 patients who reported fits had collectively paid a total of 75 visits to the Kalafong Clinic. On the occasion of each visit, one blood sample was taken per patient. Of these samples, the measured serum carbamazepine concentration of 36 was found to lie within the range of 4µg/ml to 12µg/ml, while that of the remainder (36 samples) did not. Nevertheless, in another assessment, ("Compliant concentrations" see page 20 for how it was determined) only 5 (19.2%) of the 26 patients were regarded as having serum carbamazepine concentrations which indicate compliance. (Table 9 and also Appendix Ci).

Table 9: Affinity between reported fits, measured serum carbamazepine concentrations and "Compliant Concentration"

	REPORTED FITS (F) MEASURED SERUM CARBAMAZEPINE CONCENTRATION WITHIN RANGE (YES/NO)						
Patient's Study ID	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**"Compliant Concentration"**
2	No	No	Yes (7.22)	No	Yes	No (F) (2.78)	Yes
5	No (F) (13.38)	No	No (F) (14.91)	No (F) (16.78)			No
7	Yes	Yes (F) (7.28)	Yes (F) (4.49)	Yes			No
9	No (F) (2.94)	No	No	Yes			Yes
10	Yes	Yes (F) (9.1)	Yes				No
13	Yes (F) (4.16)	Yes (F) (4.87)	No	Yes			Yes
19	Yes	Yes	Yes	Yes (F) (10.0)			No
21	Yes (F) (10.37)	Yes	Yes	Yes			No
23	No	No (F) (14.43)	No (F) (16.66)	No			No
24	Yes (F) (7.28)	Yes	Yes				No
25	MV	Yes (F) (6.66)					No
26	MV (F)	Yes (F) (10.37)					Yes
30	No	No (F) (1.78)	Yes				No
34	Yes (F) (6.96)	No (F) (1.86)	No				No
35	Yes (F) (5.03)	Yes (F) (4.55)					No
38	Yes (F) (8.84)	No	No				No
41	Yes (F) (11.08)	No (F) (1.45)	No				No
42	No (F) (<0.50)	No (F (<0.50)					No
43	No	No (F) (<0.50)					No
44	No (F) (1.07)	Yes					Yes
47	No (F) (<0.50)	No (F) (<0.50)					No

48	No	No (F) (1.10)					No
50	No	No (F) (3.11)					Yes
51	Yes (F) (10.63)	Yes					No
54	MV	No (F) (3.36)					No
68	Yes (F) (5.03)						Yes

3 Missing values (mv)

(F): Reported having had seizures since their last issue of medication

Yes = measured serum carbamazepine concentration within the range

No = measured serum carbamazepine concentration outside the range

Measured concentration (mg/L) at the visit when a fit was reported are provided in brackets

"Compliant concentration": Yes, if the measured concentration correlates with the expected concentration. No, if there is no correlation. Please see page 19 for a full explanation of the compliant concentration.

Not all the patients paid the same number of visits to the Kalafong Hospital the number of visits per patient varied from one to six. This also prevents any clear inferences on the influence of counselling on compliance and number of fits.

As a seizure/fit could have occurred any time during the month preceding the visit it was not possible to correlate the measured concentration or compliance with the time of fit. It is however a concern that 19 (53%) of the 36 concentration were outside the therapeutic range. Another six concentrations (17%) were in the lower end (below 6 mg/mL) of the therapeutic range.

Table 10: Serum Carbamazepine Concentration Expected

	Carbamazepine Expected, µg/ml
N	77
Mean	4.44
Standard deviation	2.42
Median	3.99
Minimum / Maximum	0.83 / 15.15

1 Missing value

Table 11: Serum Carbamazepine Concentration Measured

	Carbamazepine Measured, µg/ml
N	77
Mean	6.03
Standard deviation	3.51
Median	5.71
Minimum / Maximum	0.50 / 15.65

1 Missing value

The correlation between the expected and measured serum carbamazepine concentrations is not statistically significant (p = 0.062).

DRUG INTERACTION

Twenty-five patients reported that they were undergoing concomitant therapy in addition to their Tegretol®CR AED therapy. The drugs concerned were Sodium valproate (Epilim), Fluoxetine (Prozac), Phenobarbital and Phenytoin. Reference to Patsalos & Perucca (2003a) and the South African Medicines Formulary (9th ed. 2010) indicated that these drugs could affect the serum carbamazepine concentration of patients being treated with Tegretol®CR and Table 12 was therefore compiled to indicate the nature of these drug interactions.

Table 12: Drug interactions

Patient Number	Concomitant AED Medication	Mean daily dose of Tegretol®CR (mg)	Mean serum Carbamazepine concentrations		Effect of concomitant medication on serum carbamazepine concentration	
			Measured (µg/ml)	Expected (µg/ml)	Expected	Actual
5	Sodium valproate	1200	14.69	4.63	↑	↑
6	Sodium valproate	1600	8.40	6.41	↑	↑
7	Sodium valproate	400	5.73	1.89	↑	↑
15	Sodium valproate	1133	12.82	4.72	↑	↑
16	Sodium valproate	1200	7.40	5.26	↑	↑
19	Sodium valproate	800	8.49	5.38	↑	↑
24	Sodium valproate	800	7.12	3.47	↑	↑
26	Sodium valproate	1600	10.37	15.15	↑	↓
28	Sodium valproate	400	4.53	5.56	↑	↓
41	Sodium valproate	1267	8.35	2.08	↑	↑
43	Sodium valproate	400	< 0.50	3.47	↑	↓
49	Sodium valproate	800	7.14	4.90	↑	↑
71	Sodium valproate	-	7.97	3.60	↑	↑
9	Sod valproate & Phenobarb	400	3.93	1.75	↑↓	↑
12	Sod valproate & Phenytoin	800	8.72	4.17	↑↓	↑
13	Sod valproate & Phenytoin	800	4.33	4.69	↑↓	↓
14	Sod valproate & Phenytoin	400	1.06	2.56	↑↓	↓
22	Sod valproate & Phenytoin	800	9.22	6.67	↑↓	↑
33	Sod valproate & Phenytoin	1200	5.17	7.14	↑↓	↓
38	Sod valproate & Phenytoin	800	4.37	5.56	↑↓	↑
20	Fluoxetine	800	5.71	6.39	↓	↓
2	Phenytoin	1100	6.00	7.05	↓	↓
25	Phenytoin	600	6.66	2.94	↓	↑
31	Phenytoin	1600	7.06	7.41	↓	↓
39	Phenytoin	400	8.51	3.14	↓	↑

Thirteen patients were receiving both Tegretol®CR and Sodium valproate concomitantly. The collective average of their serum carbamazepine

concentrations was 7.96, therefore within the accepted optimal range of 4µg/ml to 12µg/ml. The collective average for six other patients receiving Tegretol®CR plus Sodium valproate plus Phenytoin was 5.48 µg/ml, also within the accepted optimum range. The arrows indicate the direction of the effect of the drug interaction on the patient's measured serum carbamazepine concentration (increases; ↓decreases; ↑↓= respective increase/decrease). The agreement between the expected and actual serum carbamazepine concentrations in Table 12 was found to be statistically significant (Fisher exact test, p=0.007).

INDICATORS OF COMPLIANCE

TABLES 13, 14 and 15 – *Visits* and *Serum Carbamazepine Concentrations* as Indicators.

In the search for valid indicators of compliance and non-compliance in the Kalafong study, initially only two possible indicators appeared to possess potential, viz. regular scheduled visits to the clinics at Kalafong Hospital, and serum carbamazepine concentration. Both, but serum carbamazepine concentration in particular, also have significant deficiencies as indicators. These notwithstanding, Tables 13, 14 and 15 were compiled to illustrate their possible influence. The very poor agreement between Visits and Concentration (8.2% - Table 15) is particularly notable.

Table 13: Visits as indicators of compliance

VISITS AS INDICATORS OF COMPLIANCE	
Assessment of Visit	**Number of visits (%)**
Yes	52 (66.7)
No	11 (14.1)
Uncertain	15 (19.2)
Missing values	Nil
N	78

Two out of every three visits (66.7%; 95% CI 55.6% – 76.1%) complied with the definition of a "compliant visit". "Uncertain" values occur where the numbers of "Yes" and "No" are equal, thereby preventing an equivocal classification as either *Yes* or *No*.

Table 14: Serum carbamazepine concentrations as indicators of compliance

SERUM CONCENTRATIONS AS INDICATORS OF COMPLIANCE			
Serum carbamazepine Concentration		**"Compliant Concentration"**	
Assessment	**Number (%)**	**Assessment**	**Number (%)**
Yes	41 (52.6*)	Yes	20 (25.6**)
No	32 (41.0)	No	40 (51.3)
Uncertain/missing	5 (6.4)	Uncertain	18 (23.1)
N	78 (100.00)	n	78 (99.99)

* 95% CI is 38.3% - 60.4% ** 95% CI is 18.1% - 38.5%

Uncertain values occur when the numbers of "Yes" and "No" are equal or missing values.

Owing to the deficiencies inherent in the measured serum carbamazepine concentration when it is used as an indicator of compliance, recourse was taken to what is termed in this dissertation the "*compliant concentration*".

The compliant concentration takes the time of last dose, blood specimen elapsed time after dose (position on the concentration-time graph) and possible influences of interactions with concomitant drugs into account and then correlates the result to the calculated expected concentration. A measured concentration is "compliant" if it correlates with the expected concentration even if it was outside the therapeutic range. However, for the level to be within the therapeutic range does not necessarily mean that the patient is compliant in taking carbamazepine regularly. Table 14 compares the different assessments produced respectively by *Measured Serum Carbamazepine Concentration* and *Compliant Concentration*, and of which, "*compliant concentration*" appears to be the stricter arbiter.

Table 15: Agreement between visits and measured serum carbamazepine concentration

Visit	Concentration	Frequency	Percent
No	No	8	10.3
No	Uncertain	1	1.3
No	Yes	2	2.6
Uncertain	No	9	11.5
Uncertain	Uncertain	3	3.9
Uncertain	Yes	3	3.9
Yes	No	23	29.5
Yes	Uncertain	14	17.9
Yes	Yes	15	19.2
Agreement between visits and concentration is: = 15/78 = 19.2%			

CHAPTER 5. DISCUSSION

INTRODUCTION

As mentioned in Chapter 1, one intention of the Kalafong study was to examine the efficacy of monitoring serum carbamazepine concentrations in the determination of the compliance or otherwise displayed by a heterogeneous group of adult outpatients. These patients were epileptics who were undergoing treatment with one of three forms of the carbamazepine drug. The contribution made by counselling towards promoting compliance was also to be explored.

The objectives of the study were therefore the following:

To determine individual measured serum carbamazepine concentrations at four consecutive 28-day intervals in a heterogeneous population of outpatients being treated for epilepsy. On such occasions they also received counselling.
To ascertain whether these concentrations can be correlated with compliance or non-compliance, with due regard to relevant matters such as pill counts, age, gender and concomitant drug interactions.
To explore whether counselling makes for better compliance.

It has been frequently mentioned in the relevant literature that the definition of compliance is not a straightforward matter. In keeping with other workers (Buck *et al.* (1997); Lui *et al.* (2003); Specht *et al*. (2003); Pellock *et al*. (2004) and Cramer (2006)) the definition used in the Kalafong study embraced a number of aspects. These were, *inter alia*, taking the correct dosage, observing the correct interval between doses, and taking the medication for the full duration of the period specified, but also included material behavioural changes. However, just as an exact definition of compliance could be problematic, so also can be its detection and measurement. Buck and her co-workers (1997) mention patients' reports, pill counts, blood tests, the outcomes, and the conclusions of those who tend these patients, all as relevant elements.
Regular, formal questioning of certain patients who were involved in this study and were undergoing anti-epileptic therapy at Kalafong Hospital revealed that non-

compliance with their medication prescriptions was relatively common amongst them. Some stopped because they believed that they had been cured, others interrupted or stopped their medication because they experienced unpleasant effects, others forgot to take their tablets several times a month, and yet others did not fully understand the instructions that they were given.

INDICATORS OF COMPLIANCE

The search for valid indicators of compliance initially yielded little of significance. Much of the published research focused on inpatients where dosage is given at prescribed times, all seizures are witnessed and their times noted, and any blood samples can be taken at the appropriate position on the serum concentration/time curve.

In the Kalafong study, initially and being influenced by published research, serum carbamazepine concentration, the non-occurrence of seizures and conscientious attendance at the respective Kalafong Hospital clinics, were regarded as possible indicators of compliance. However, in the light of experience acquired as the study proceeded, attendance (visits) and (with reservations) serum carbamazepine concentration, and later, “Compliant Concentration” also, became preferred as possible indicators of compliance/non-compliance.

Attendance (visits) proved to be a relatively usable indicator (Table 13; Table 15). Bearing in mind the logistic constraints affecting an outpatient, any visit to the Kalafong Hospital which took place within a period two days before to two days after due date was regarded by the researcher as indicating compliance.

Two out of three (66.67%) of the patients qualified in this regard (“compliant visits” Table 13).

Serum carbamazepine concentration is regarded by a number of workers as a simple yet useful method of detecting or ruling out irregular intake patterns of patients’ medication (Eadie (1998); Specht *et al*. (2003); Tomson *et al*. (2010);

Yukawe (1996)). Eadie (1998) states that TDM is currently reasonably efficient and relatively satisfactory.

The relationship between serum carbamazepine concentration and compliance is, however, tenuous. Having serum carbamazepine within the accepted range (4µg/ml to 12µg/ml) does not necessarily make the patient compliant (Appendix Ci). For example, a patient receiving a sub-therapeutic dose of Tegretol®CR may be fully compliant and take his/her medication conscientiously as prescribed, but may not present with a serum carbamazepine concentration within the range, owing to sub-therapeutic dosage. In similar vein, a non-compliant patient who is receiving an excessive dose of Tegretol ®CR may, by virtue of a consequent high serum carbamazepine concentration, present as being compliant. The time elapsing between the last dose of Tegretol ®CR and the drawing of the blood sample, *ie.* where it is taken on the patient's serum concentration/time curve, needs to be consistent and optimal. Possible drug interaction must also be considered. Finally, the inherent variability of patients with regard to their individual responses to medication must also be established.

Being aware of the constraints entailed in the use of serum carbamazepine concentration as an indicator in the Kalafong study, but also being mindful of the opinions expressed by other workers, albeit in respect of studies under markedly different conditions, it was decided to pursue the role of serum concentration as an indicator a little further (Appendices Ci and Cii; Tables 13, 14 and 15). Table 14 shows, for example, that, at best, only 52.6% of the participants in the study could have been compliant, or, at least, had serum carbamazepine concentrations within the 4 µg/ml to 12µg/ml range.

DEMOGRAPHICS

Studies of compliance carried out in Germany (Specht *et al*. (2003)), Singapore (Tan *et al.* (2005)), Taiwan (Lui *et al*. (2003)), the United States of America (Cramer (2006)) and the United Kingdom (Patsalos *et al.* (2003 a)) have been considered and their results in respect of the patients concerned, primarily in-patients of these countries, noted. It is however, important to recognise the cultural

differences that exist between these countries and South Africa. The totally different African traditions and culture may possibly require different techniques, strategies and solutions, notwithstanding the similarities in the universal problem. Struwig & Stead (2003) remind us that research does not occur in a vacuum but is intimately bound to socio-historical, temporal and contextual factors. In the Kalafong data, therefore, we should explore a link between demographics such as gender, age and weight, and compliance.

GENDER OF PATIENTS

Data in respect of the gender of the patients are presented in Table 1 and Table 2. It will be seen that 50 (64.1%) of the 78 patients were male and 28 (35.9%) were female. The recruiting of patients for this study was done as patients became available, which occurred in a random fashion, the preponderance of males notwithstanding. Gender had no significant effect on compliance, whether the indicator used was visits or measured serum concentration (Table 2). The data of Table 2 indicate that, when visits were used as an indicator of compliance, females (95%) were more compliant than males (76.7%) of their visits could be classified as compliant). However, when serum carbamazepine concentration was so used, the position was reversed.

Buck *et al*. (1997) and Specht *et al*. (2003) also found that gender was not a factor significantly affecting compliance in their investigations. Although 53% of the respondents in their study were female, Doughty *et al*. (2003) also do not mention any significant effect due to gender.

AGES OF PATIENTS

Taken collectively, the ages of the patients of the Kalafong group ranged from 16 to 68 years. The individual ages of these patients were grouped into incremental 15-year class intervals (Table 3; Table 4). The majority of the patients (93.3%) were younger than 60 years of age, with 60% of the under-sixties being only 45 years old or younger. The mean age of the group used for the study was 42.5 years, with a median group age of 43 years, these values suggesting that, age-wise, the group was well balanced.

In published studies of factors influencing the degree of compliance with anti-epileptic drug regimes, the age of the patient has not escaped attention. Buck *et al*. (1997) identified seven factors which showed a univariate association with degree of compliance, one such factor being the age of the patient. In a further, multivariate analysis, Buck and her co-workers (1997) found that either being a teenager or otherwise being aged under 60 were amongst the strongest predictors of non-compliance in their study. Age, as previously mentioned (Table 4), did not play a significant role.

In their introductory remarks, Specht *et al*. (2003) state “adolescents and young adults seem to constitute a subgroup with a higher risk for non-compliance”. However, in their presentation of the results of their study they state that “there was no significant difference between compliant and non-compliant patients with regard to sex, age, duration of epilepsy, and interval between index seizure and previous seizure”. The mean patient age in their study was 20.6 years.

Patsolos & Perruca (2003a) regard age as an important source of variability in the susceptibility of older patients to drug interactions, elderly patients being more susceptible to metabolic reactions. These workers do, however, mention that a recent study showed no evidence of reduced responsiveness to enzyme induction in elderly patients treated with carbamazepine. As there were only 5 patients >60 years old in the Kalafong study, these perceptions may not be of practical importance.

Doughty *et al.* (2003) found that being a teenager or otherwise <60 years old were amongst the key predictors of non-compliance in their assessment of compliance when patients were switched from an immediate-release to a sustained-release AED formulation.

The findings of these workers notwithstanding, in the Kalafong study no significant link between age and compliance was detected (Table 4).

WEIGHTS OF PATIENTS

Seen against the lack of significant differences in the data presented in Table 6: *Effect of weight on compliance*, the only further significance of the weight of the patient in so far as the Kalafong study was concerned was it use as a factor (W) in the formula:

$$C = \frac{D \times F \times S}{Cl \times Wt \times 24}$$

which was used in the calculations of the expected serum carbamazepine concentrations (Appendix Ci; Table 10). The data of Table 6 do not, however, indicate, any affinity between patient's weight and compliance.

MEAN DAILY DOSE

The daily dose of Tegretol®CR prescribed for patients in the Kalafong study varied from 200mg to 1600mg (Appendix Ci; Table 7). One or more changes were prescribed during the study period to the daily doses of eight of the group, thereby introducing an undesired variability in the data being assembled. Records of dosage were also incomplete in the case of another 14 patients, thereby exacerbating the variability being introduced into some of the data. This, and a considerable amount of missing data which could not be traced, precluded the employment of logistic regression and other such statistical analysis and obliged the researcher to resort to descriptive statistics only. For these reasons, also, it was decided to use the means of the daily doses prescribed.

The largest sub-group comprised 30 patients (44.1%) and each of these patients received a daily dose of between 400mg and 800mg. Twenty-five patients of the population were also taking other AEDs as well, while yet others were also undergoing treatment for illnesses other than epilepsy and were taking the appropriate concomitant medication.

The range (200 mg to 1600 mg) of the doses given to the Kalafong study group also clearly illustrates the inherent variability of the patients with regard to their individual responses to medication (Patsalos & Perucca (2003 a)).

BREAK-THROUGH SEIZURES (FITS)

The occurrence of break-through seizures is often held by some researchers to be the result of poor compliance (Buck *et al*. (1997); Cramer *et al*. (2002); Doughty *et al*. (2003); and others). Indeed, Specht *et al*. (2003) regarded non-compliance as a major cause of inadequate seizure control.

For example, the PPPF of Tan *et al*. (2005) were implicated in three-quarters of the seizure-related hospital admissions of epileptic patients in Singapore. (These factors are: non-compliance (71%), sub-therapeutic dosage (*ipso facto* sub-minimal serum carbamazepine concentration) – 26%, and deprivation of sleep).

It may therefore not be wholly unreasonable to infer from these particular excerpts from the literature concerned, that the following relatively simplistic relationship exists: *poor compliance leads to low serum carbamazepine concentrations, which in turn lead to break-through seizures*.

Is this, however, completely valid? The Kalafong data indicate that a fit should not automatically be considered as an indication that a patient has not been compliant as the fit could have taken place during the month preceding the visit and not at the time the concentrations were measured. Due to the selection of patients attending the outpatient clinic it was not possible to include patients who had recently a seizure as such patients would be seen at casually department and not at the outpatient department. After having a seizure patients may also increasing their dose particularly if they knew they were non-compliant.

The relevant results of the Kalafong study are presented in Tables 8 and 9. Table 8 indicates that 26 (33.3%) of the 78 patients in the Kalafong study (one in three) reported having had fits. The mean measured serum carbamazepine concentrations of 19 of the 26 (53.9%) were, however, outside the accepted therapeutic range (4µg/ml to 12µg/ml) (Table 9). When the “Compliant Concentration” is used as a measuring tool, however, (Table 9, Appendix Ci, Appendix Cii), only 7 (27%) of the 26 were regarded as having serum carbamazepine concentrations which indicated compliance. The Kalafong data in

respect of seizures indicate that the relationship between seizures and compliance is not a simple one and that the occurrence or otherwise of break-through seizures should not be automatically used as an indicator of compliance as a wrong dose may also be the reason.

EXPECTED AND MEASURED SERUM CONCENTRATIONS

No correlation was found between the data of the expected and the measured serum carbamazepine concentrations (Fisher Exact Test: $p = 0.062$). The variability of the data concerned could have contributed to this.

DRUG INTERACTION

In the Kalafong study, dosage regimen varied from monotherapy with carbamazepine (Tegretol®CR) for some patients, through polytherapy with a combination of two or more AEDs of which carbamazepine was one, for other patients, to polytherapy with a combination of carbamazepine with drugs prescribed for the management of other disorders.

Interaction between carbamazepine and drugs prescribed for epilepsy and co-existing disorders other than epilepsy, has enjoyed the attention of, *inter alia*, the editors of a number of manuals, amongst others Beer & Berkow (1999); di Piro, Talbert, Yee, Matzke, Wills & Posey (2002); Rossitor (2010) and Turner (2001).

In the first part of their review of clinically important drug interactions in epilepsy, Patsalos & Perucca (2003 a) summarised *inter alia*, the main mechanisms of drug interactions and highlighted the more important interactions between AED's.

Interactions between AED's and drugs prescribed for the management of other disorders were discussed in part two of their review (Patsalos & Perucca 2003 b).

For AED's, pharmacokinetic interactions (ie those involving the absorption, distribution or elimination of the drug) are regarded by these authors as the most notable, but pharmacodynamic interactions (which take place at the site of action

and result in a modification of pharmacological effects without any change in the drug concentrations in the serum) are also important (Patsalos & Perucca 2003 a).

In the Kalafong Study, where the efficacy of monitoring serum carbamazepine concentrations for the determination of compliance is a cardinal consideration, the potential interaction between AED's and other drugs taken concurrently, can therefore not be ignored.

Twenty-five patients (32.05% of the 78 used in the Kalafong study) reported that they were undergoing concomitant dosage in addition to their Tegretol®CR therapy. The drugs concerned were Sodium valproate (Epilim), Fluoxetine (Prozac), Phenobarbital and Phenytoin. Reference to Patsalos & Perucca (2003 a) and the South African Medicines Formulary (9th ed. 2010) indicated that these drugs could affect the serum carbamazepine concentration of the patients treated with Tegretol®CR. The drug interaction concerned is presented in Table 12.

Table 12 indicates that the mean serum carbamazepine concentration of three patients receiving Sodium valproate together with Tegretol®CR, and three other patients receiving Phenytoin together with Tegretol®CR, did not follow the expected direction of interaction. In the case of the remaining 19 patients the interaction was as expected.

Drug interaction must therefore be acknowledged when evaluating serum carbamazepine values, and it must also be correctly interpreted.

COUNSELLING

The importance of convincing the patient that it is vital to take his or her medication strictly as prescribed has been mentioned by several research workers (Lui *et al*. (2003)), Pellock *et al*. (2004), and others) and also Cramer (2006) who states that "teaching patients how to take their medicine is probably more important than explaining mechanisms of action".

According to Lui *et al*. (2003), conventional verbal education (counselling) of the patient can achieve good compliance, but it may not adequately cover drug-related issues and the consequent lack of AED knowledge, in its turn, can result in decreased patient compliance, which is a serious hindrance to successful treatment. They also state that providing patients with written information "apparently" increased their knowledge of their medication and "probably" enhanced control of seizures.

The positive effect of education, presumably achieved by way of counselling, is supported by the work of Buck *et al*. (1997) who mention that "further implementation of educational programmes for people with epilepsy would help to improve compliance, thereby reducing unnecessary seizures".

A study by Petersen, McLean & Millingen (1984) who randomly allocated 53 epileptic hospital outpatients to either a control or an intervention group, and then subjected the intervention group to a combination of compliance-improving strategies, supports the contention of Buck *et al*. (1997). Both patient compliance and clinical control improved significantly in the patients of their intervention group.

As mentioned in Chapter 3: *Methodology*, the outpatients selected for the Kalafong study were given, at four consecutive 28-day intervals, sufficient tablets for 28 days' medication with the form of carbamazepine and other medicine which had been prescribed for them at that time. They were required to collect these tablets personally from the Kalafong Hospital pharmacy and to undergo a standard counselling on each such occasion. The counselling was done by the researcher responsible for the Kalafong study and every patient was counselled according to the prescribed procedure. The patients appeared to appreciate the counselling and showed willing co-operation when it came to presenting themselves for the individual counselling sessions.

Improved compliance was the outcome expected from the counselling. The challenge was to quantify the levels of compliance achieved as the study proceeded. Peterson *et al*. (1984) used, *inter alia*, serum AED levels, frequency of

seizures and the regularity of patient visits for prescription repeats to quantify the improvement they had detected in compliance. They report a halving of seizure frequency in their intervention group as well as improved attendance of clinic appointments and enhanced patient compliance.

Twenty-six patients (33.3% of the Kalafong study group) reported break-through seizures during the period of the study and 66.6% did not report seizures. The mean measured serum carbamazepine concentrations of 19 of the 26 (53.9%) were, however, outside the accepted therapeutic range (4µg/ml to 12µg/ml) (Table 9). When the "Compliant Concentration" is used as a measuring tool, however, (Table 9, Appendix Ci, Appendix Cii), only 7 (27%) of the 26 were regarded as having serum carbamazepine concentrations which indicated compliance.

Several workers, *inter alia* Lui *et al*. (2003), Pellock *et al*. (2004) and Cramer (2006) regard counselling as being more than the conventional verbal education as was done in the Kalafong study. They mention the placing of information posters in strategic positions, illustrated posters which catch the eye, information broadcasts in reception halls, *ad hoc* demonstrations to assembled waiting patients, educational programmers for epileptics, etc. For counselling to be able to play its rightful role, future counselling of epileptic outpatients at Kalafong will need to include such interventions.

In retrospect, the attempt to explore whether counselling tended to make the Kalafong patients more compliant, did not succeed to the extent hoped for. Using visits as an indicator showed that 66.67% (two in three) could be regarded as being compliant. (Table 13). For various reasons which have been discussed earlier, serum carbamazepine concentration had potential deficiencies as an indicator of compliance, but nevertheless indicated that 37 (49.33%) of the patients were compliant. (Table 14). It was initially expected that counselling would produce better compliance but it was not possible to measure any improvement in compliance, and it was therefore not possible to define the role played by counselling.

COMPLIANCE

McPhee & Pignone (2005) mention that the successful treatment of many illnesses depends on the acceptance by the patient of fundamental behavioural changes such as, *inter alia*, alterations in diet, giving up smoking, taking up exercise, and adherence to medication regimes. They state that compliance is a problem in every practice, with up to 50% of patients not achieving full compliance.

Poor compliance has been described as a major problem in epilepsy therapy by several other research workers also. Buck *et al*. (1997), addressing strategies such as special electronic medicine container/dispensers, and self-recording of both medicine-intake and the occurrence of seizures, state that "even with sophisticated methods there is no guarantee that pills are actually taken (by outpatients)" and they also mention that, with regard to the so-called pill counts, "patients empty out pills without actually taking them". A touch of desperation is evident in their statement that "the only sure way is if the physician stands guard every time doses are due".

However, Joyce Cramer (2006) regards most patients as falling into the category "partial" or intermittent compliance. She believes that compliance is inversely related to the number of doses prescribed per day and advises those concerned to "think again about simple dosing regimens and the need to combine everything (including concomitant medication) into a couple of convenient times a day".

The objectives of the Kalafong study all focus ultimately on compliance in epilepsy control. Pursuant to the attained objective of determining the individual measured serum carbamazepine concentrations of 78 Kalafong epileptic outpatients at four consecutive 28-day intervals (Appendix Ci), came the second objective, *viz* to explore whether these concentrations could be correlated with compliance. A third objective was to explore whether counselling makes for better compliance.

The respective results of the Kalafong study and derived from the data presented in Appendices Ci and Cii, have been presented in Tables 1 to 15 and duly

discussed. Gender (Tables 1 and 2), age (Tables 3 and 4), and weight of the patient (Tables 5 and 6) were not significantly associated with compliance.

Several researchers (Buck *et al*. (1997); Cramer *et al*. (2002); Doughty *et al*. (2003); Specht *et al*. (2003) and Tan *et al*. (2005), amongst others) regarded the occurrence of break-through seizures as an indication of non-compliance. The Kalafong data in respect of seizures indicate, however, that the relationship between seizures and compliance is not a simple one and that the occurrence or otherwise of break-through seizures could not automatically be used as an indicator of compliance (Tables 8 and 9; Appendices Ci and Cii).

In the Kalafong search for valid indicators of compliance or non-compliance, only two possible indicators eventually appeared to possess any potential in this regard. One was that the patient should have conscientiously paid punctual, regular scheduled visits to the Kalafong Hospital clinics. However, for reasons discussed previously, this did not prove to be an infallible indicator of compliance. Serum carbamazepine concentration was the other possible indicator, but as also discussed previously, it suffers from material deficiencies in such role. For example, where doses are sub-therapeutic, notwithstanding full compliance, measured serum carbamazepine concentrations may indicate a lack of compliance. Where doses are excessive, but compliance is lacking, the serum carbamazepine concentration could nevertheless indicate adequate concentration.

However, using punctual, regular, scheduled visits to the Kalafong Hospital clinics as an indicator of compliance, only 52 (66.67%) of the 78 epileptic outpatients could be categorized as being compliant over that period (Table 13).

Using measured serum carbamazepine concentration within the accepted range of 4µg/ml to 12 µg/ml, as an indicator, only 37 of 75 epileptic outpatients (49.33%) could be so categorised (Table 14).

In each case the 95% Confidence Interval (CI) was applicable. Nevertheless, the agreement between visits and concentration was 19.2% (Table 15).

It is therefore doubtful whether measured serum carbamazepine can be used as a reliable indicator of a patient's compliance. Certain factors, *viz*

adequacy or otherwise of patient's medication,

variable times between last dose and drawing blood,

drug interaction, and

inherent variability of the individual patient in his/her response to medication, could give rise to spurious indications and such potential problems would have to be solved before considering measured serum concentration as usable. However the "Compliant Concentration" takes these factors into account and thereafter correlates the resulting values with the calculated "expected concentration". A concentration is "compliant" if it can be correlated with the *expected correlation*, its therapeutic range notwithstanding.

CHAPTER 6. SUMMARY AND CONCLUSIONS

INTRODUCTION

In epilepsy therapy, non-compliance in respect of the patient's prescribed medication regimen is mentioned by several research workers as a major factor in inadequate seizure control (Buck *et al*. (1997); Cramer (2006; Lui *et al*. (2003); Pellock *et al*. and others)). Furthermore, non-compliance is said to be closely interlinked with what certain workers regard as a less than optimal serum anti-epileptic drug concentration (Eadie (1998); Specht *et al*. (2003)) *inter alia)*.

A study was undertaken at the Kalafong Hospital to examine the efficacy of monitoring, by means of the TD_xFL_x System (ABBOTT), serum carbamazepine concentrations for the determination of compliance by a group of 78 epileptic outpatients. The contribution made by counselling towards promoting such compliance was also explored, but the results could not be quantified and assessed.

The objectives of the study were the following:

To determine individual measured serum carbamazepine concentrations at four consecutive 28-day intervals, in a heterogeneous group of outpatients being treated for epilepsy, on which occasions they would also receive counselling.

To ascertain whether such concentrations could be correlated with compliance or non-compliance, with due regard to relevant matters such as, inter alia, pill counts, fit chart records and predictor variables such as age, gender, patient weight and concomitant drug interaction.

To explore whether counselling makes for better compliance.

CONSTRAINTS

Shortly after the study was launched, several unforeseen constraints emerged. Being outpatients, the participants were not under continuous supervision and care, and the taking of their medication lay entirely in their own hands. They had to arrange and finance their travel to and from the hospital and the irregular availability of such taxis as were at their disposal made their attendance at

stipulated times problematic. At times they sent their children to collect their next issue of AED, thereby breaking the continuity of the patient's counselling. A chronic shortage of trained staff existed at Kalafong Hospital and therefore delays in consultations and in the taking of blood samples were inevitable. Finally, the time elapsing between the patient's last dose of Tegretol®CR and the blood sampling was dictated by circumstances and was therefore inevitably variable.

INDICATORS OF COMPLIANCE

The search for valid indicators of compliance initially yielded little of consequence. In the light of experience gained as the study proceeded, however, attendance of the clinics at Kalafong, and (with reservations) measured serum carbamazepine concentration, were focused on as possible indicators of compliance in this study. Visits proved, however, to be a somewhat weak indicator, and measured serum carbamazepine even more so. The correlation between these two indicators was also very poor (8.2%). The data on expected and measured serum carbamazepine concentration were therefore reinforced by utilising *Compliant Concentrations* (Appendix Ci) which, *inter alia*, take the elapsed time between the last dose taken and the drawing of the blood sample, into consideration; they also take interaction between carbamazepine and concomitant drugs into account, and correlate with the expected concentration.

GENDER

(Tables 1 and 2)

Males (64.1%) of the study population) outnumbered females. The collective compliance rates as indicated by visits (82.5%) and serum carbamazepine concentration (56.2%) do not differ significantly (Fisher Exact Test: $p = 0.716$). Gender therefore had no significant influence on compliance.

AGE

(Tables 3 and 4)

The majority (93.3%) of participants were younger than 60 years of age, and 60% of these were 45 years old or younger. For both modes of assessment (visits and

measured serum carbamazepine concentration), no association/affinity was found between compliance and age. (Fisher Exact Test: p = 0.990 (visits) and 0.282 (concentration). Age therefore had no significant influence on compliance.

WEIGHT

(Tables 5 and 6)

Fifty percent of the patients fell into the weight group 60 kg to 80 kg. The mean weight was 71.86 kg and the median weight 70 kg. For both modes of assessment (visits and serum carbamazepine concentration, respectively) there was no affinity between patient's weight and compliance. (p (visits) = 0.987; p (serum carbamazepine concentration) = 0.848).

MEAN DAILY DOSE AND DRUG INTERACTION

(Tables 7 and 12)

The daily dose of Tegretol®CR prescribed for patients of the study ranged from 200mg to 1600mg; 44.1% of the patient population received a daily dose ranging from 400mg to 800mg. The wide range (200mg to 1600mg) of the daily doses given to the study group illustrates their inherent variability with regard to medication. (Table 7).

Twenty-five patients (32.05% of the group) were also undergoing concomitant dosage with other AED's in addition to their Tegretol®CR therapy. In the case of 19 of these patients the drug interaction was as expected (Fisher Exact Test: p = 0.007). (Table 12).

BREAK-THROUGH SEIZURES

(Tables 8 and 9)

One in three (26 patients, ie 33.33% of the study group) reported having had seizures during the study period. The serum carbamazepine concentrations of 19 (73.1% of the 26) of these fell within the accepted range (4µg/ml to 12µg/ml), while the remaining 7 patients (26.9%) presented with concentrations outside the accepted range. Using the *"Compliant Concentration*" (Appendix Ci) as a measuring tool, however, indicated that only 5 of these 26 patients were compliant.

The Kalafong data in respect of seizures therefore indicate that the relationship between seizures and compliance is not a simple one and that the occurrence or otherwise of break-through seizures should not be used as an indicator of compliance.

SERUM CONCENTRATION EXPECTED AND MEASURED

(Tables 10 and 11)

The correlation between the expected and measured serum carbamazepine concentrations was not statistically significant (Fisher Exact Test: $p = 0.062$). The calculated expected serum carbamazepine concentration was a factor of some significance however, because of the correlation sought in the calculation of the "Compliant Concentration".

COUNSELLING

It was initially expected that counselling would produce better compliance, but it was not possible to measure any change in this regard and it was therefore not possible to define the role played by counselling. It is however clear that the conventional verbal counselling as was done in the Kalafong study did not improve compliance nor decrease the number of fits and need to be enhanced by several supporting interventions which are being utilised by other workers.

GENERAL

Beneficial studies of compliance have been carried out in widely-differing countries such as Germany, Singapore, Taiwan, the United States of America and the United Kingdom. Notwithstanding the similarities in the universal problem of epilepsy and ample evidence that compliance with the prescribed medication regimen is an important issue, the totally different African tradition regimens and culture nevertheless appear on occasion, to need different therapeutic techniques, strategies and solutions.

Therefore when evaluating the outcomes of the Kalafong study, the results achieved, whether positive or negative, should be seen within the environment in which the study was carried out. Much of the published international research

deals with in-patients where strict control and supervision was implemented. The participants in the Kalafong study were out-patients and compliance with their medication regimen lay entirely within their own hands, while environmental factors such as transportation and resources often operated negatively.

The three objectives of the study were consistently addressed, but some outcomes, particularly those with regard to counselling, were less than successful. On the whole, however, the Kalafong study provides useful guidelines for future studies of this kind in the African environment.

CHAPTER 7. RECOMMENDATIONS

The Kalafong study high-lighted certain matters, in respect of which the following recommendations are offered.

ADAPTING THE RESEARCH TECHNIQUES TO THE RESEARCH ENVIRONMENT

When planning a study such as this, serious attention should be paid timeously to the environment and the culture within which it is to be conducted. The local traditions and way of life may possibly need different techniques, strategies and solutions, notwithstanding the similarities in the universal problem and ample evidence that multi-faceted compliance is a fundamental issue in epilepsy therapy.

COUNSELLING

The object of counselling is to motivate the patient to do the right thing in the correct way and at the right time. Intrinsic in this is a clear understanding by the patient of exactly whatever he or she is being guided to do. Whenever possible therefore, the patient should be counselled in the respective mother tongue.

Counselling must play an important role in ensuring medication compliance, at least, the many other facets of compliance notwithstanding. The effect of counselling must be measurable. This implies an ongoing campaign utilising up-to-date visual and audio aids, all at appropriate times, and thereafter, measurable, follow-up evaluation of technique.

PATIENT RESOURCES

When planning a research study, cognisance should be taken*, inter alia*, of the patient's financial resources, the availability of transportation at the prescribed times, and the possibility of the employer allowing him/her time to visit the hospital.

Such, and many other constraints often made it difficult for patients to be available during prescribed times. Furthermore, it is not unusual for parents to send their

children to collect their medicines from the hospital, thus breaking continuity of the counselling strategy.

BLOOD SAMPLING

The time elapsing between the last dose taken by the patient and the drawing of the blood sample varied from dose to dose and from patient to patient. One solution would be to admit the patient overnight, during which time the last dose and the subsequent blood sampling could occur. Neither the hospital nor the patient might be entirely enthusiastic about this, but it is nevertheless one solution.

GENERAL

A less variable group of participants should be used in the next study.

A designated nodal point in the Kalafong Hospital where epileptic patients could report for routeing to the next stage of their program in the clinic, would prevent a great deal of wasted time and speed up the flow of patients' consultations, blood sampling, etc.

The "Compliant Concentration" takes the following into account:-
Date and time of last dose of carbamazepine;
Elapsed time after last dose (i.e. position on concentration / time graph);
Any interactions with concomitant drugs; and then correlates the result to the calculated expected serum concentration. A concentration is compliant if a correlation with the expected correlation is found, even if it was outside the therapeutic range. The Compliant Concentration thereby removes the deficiencies of the measured serum carbamazepine concentration as an indicator of compliance. A future study should therefore use the Compliant Concentration instead.

REFERENCES

Beers, M.H. & Berkow, R., editors; 1999. The Merck Manual of Diagnosis and Therapy. 17th ed. New Jersey: Merck Research Laboratories.

Deborah Buck, Ann Jacoby, Baker, G.A. & Chadwick, D.W. 1997. Factors influencing compliance with anti-epileptic drug regimes. Seizure 6, 87-93.

Joyce Cramer, Glassman, M. & Rinzi, V. 2002. The relationship between poor medication compliance and seizures. Epilepsy and Behaviour 3, 338-342.

Joyce Cramer. 2006. Quoted in Neurology Reviews Com 14, 3.

Di Piro, J.T., Talbert, R.L., Yee, G.C., Matske, G.R., Wells, Barbara G., & Posey, L.M., editors; 2002. Pharmacotherapy. A Pathophysiologic Approach. 5th ed. New York: McGraw-Hill.

Julie Doughty, Baker, G.A., Ann Jacoby & Virginie Lavaud. 2003. Compliance and switching from an immediate-release to a sustained-release formulation of valproate in people with epilepsy. Epilepsy and Behaviour 4, 710-716.

Eadie, M.J. 1998. Therapeutic drug monitoring: Anti-epileptic drugs. Br. J. Clinical Phamacol 46, 185-193.

Lui, L., Yui, C.H., Yen, D.J., Chou, M.H. & Lin, M.F. 2003. Medication education for patients with epilepsy in Taiwan. Seizure 12, 473-477.

McPhee, S.J. & Pignone, M. 2005. General approach to the patient: Health maintenance and disease prevention. In: Current Medical Diagnosis and Treatment (CMDT). 44th ed. New York: McGrew-Hill.

Patsalos, P. & Perucca, A.E. 2003a. Clinically important drug interactions in epilepsy: General features and interactions between anti-epileptic drugs. The Lancet: Neurology 2, 347-356.

Pellock, J.M., Smith, M.C., Cloyd, J.C., Uthman, B. & Wilder, B.J. 2004. Extended-release formulation: simplifying strategies in the management of antiepileptic drug therapy. Epilepsy and Behaviour 5, 301-307.

Peterson, G.M., McLean, S., & Millingen, K.S. 1984. A randomised trial of strategies to improve patient compliance with anti-convulsant therapy. Epilepsia 25, 4, 412-417.

Rossitor, D. editor: 2010. South African Medicines Formulary. 9th ed. Cape Town: Health and Medical Publishing Group of S.A. Medical Association.

Specht, U., Elsner, H., May, T.W., Schimchowski, B. & Thorbecke, R. 2003. Postictal serum levels of antiepileptic drugs for detection of non-compliance. Epilepsy and Behaviour 4, 487-495.

Struwig, F.W. & Stead, G.B. 2003. Planning, Designing and Reporting Research. 2nd ed. Cape Town: Hanli Venter.

Tan, J.H., Wilder-Smith, E., Lim, E.C.H. & Ong, B.K.C. 2005. Frequency of provocative factors in epileptic patients admitted for seizures: A prospective study in Singapore. Seizure 14, 464-469.

Tomson, T., Dahl, M.L. & Kimland, E. 2010. Therapeutic monitoring of anti-epileptic drugs for epilepsy. (Review – The Cochrane Library, Issue 5, 1-16).

Leesette Turner, editor; 2001. Daily Drug Use: Essential Drug Information in Easy-to-Read Format. Revised ed. Cape Town: Cape Western Branch of Pharmaceutical Society of South Africa.

Whitehouse, W. & Morris, B. 1997. Paediatric outpatient anti-epileptic drug doses recorded in the medical charts are not reliable: Implications for the notions of non-compliance. Seizure 6, 41-42.

Yukawe, E. 1996. Optimisation of anti-epileptic drug therapy: The importance of serum drug concentration monitoring. Clinical Pharmacokinetics 31, 2.

Information Pamphlet: TD_X / TD_X FL_X Carbamazepine. 2004. IL USA: Abbott Laboratories (Reference 9515 34 – 3170 / R8).

LIST OF APPENDICES

APPENDIX A
TO DISSERTATION
R.A. BRIDGENS

KALAFONG HOSPITAL **THERAPEUTIC DRUG MONITORING**

PATIENT NAME: _____

HOSPITAL NUMBER: _____ **STUDY NUMBER:** _____

WEIGHT: _____**kg** **AGE:** _____ **DATE:** _____

DIAGNOSIS: Epilepsy

DISEASE STATUS (e.g. Renal Failure):

SERUM CREATININE: **ALBUMIN:**

<u>CARBAMAZEPINE:</u>

Dose given and interval:

Starting date of therapy:

Time of last dose: ____**h**____ **Date of last dose:** _____

Time sample drawn: ____**h**____ **Date sample drawn:** _____

Other information:

FOR TDM USE ONLY:

DRUG NAME	MEASURED CONCENTRATION	EXPECTED CONCENTRATION	THERAPEUTIC RANGE
			4 – 8 µg/ml

RECOMMENDATIONS: _____

APPENDIX B
TO DISSERTATION
R.A. BRIDGENS

Patient Name: _____

File Number: _____

FIT CHART

Date *	Current Strength, Type and Regimen *	Total fits Between Counselling Sessions *	Date of Fit *	Result of Pill Count	Plasma Carbamazepine		Blood Sent *
					Date	Value	

- **To be completed by Doctor or Pharmacist**

APPENDIX Ci

THERAPEUTIC DRUG MONITORING (2009)
(R.A. BRIDGENS)

Patient's Study No	Age	Wt kg	Daily Dose mg	Visit	Last Dose			Compliant Visits	Blood Sample			Carbamazepine Concentration				Fits
					Day	Month	Time Taken		Day	Month	Time Drawn	Measured µg/ml	Expected µg/ml	Measured Within Range	Compliant Concentration	
1	41	69	1200	1	06	03	07:00	Y	06	03	13:30	8.90	2.42	Y	N	No
			600	2	10	03	07:00	N	10	03	08:30	8.17	3.62	Y	N	No
			600	3	07	04	07:00	Y	07	04	08:55	9.26	3.62	Y	N	No
			600	4	03	06	07:00	N	03	06	11:00	11.36	3.62	Y	N	No
			600	5	01	07	07:00	Y	01	07	10:00	12.49	3.62	N	N	No
2	34	65	600	1	17	03	15:00	Y	17	03	16:05	DI 1.97	3.85	N	Y	No
			1600	2	01	04	07:00	N	01	04	11:00	↓ 2.78	10.26	N	N	No
			1000	3	12	05	06:30	N	12	05	08:55	↓ 7.22	6.41	Y	Y	No
			1600	4	27	05	07:15	N	27	05	12:05	↓ 16.66	10.26	N	N	No
			1000	5	09	06	07:00	N	09	06	09:30	↓ 4.61	6.41	Y	Y	No
			800	6	14	07	07:00	N	14	07	11:00	↓ 2.78	5.13	N	Y	Yes
3	54	56	800	1	09	03	08:00	Y	09	03	12:00	9.67	5.95	Y	N	No
			1200	2	06	04	06:00	Y	06	04	14:30	<0.50	8.93	N	N	No
			800	3	03	05	06:00	Y	03	05	14:00	<0.50	5.95	N	N	No
			800	4	31	05	18:00	Y	01	06	10:00	2.04	5.95	N	N	No
			800	5	29	06	06:00	Y	29	06	11:05	14.19	5.95	N	N	No
4	52	58	400	1	01	04	08:00	Y	01	04	08:55	3.67	2.87	N	Y	No
			400	2	28	04	08:00	Y	28	04	08:50	1.95	2.87	N	Y	No
			400	3	27	05	08:00	Y	27	05	09:15	1.91	2.87	N	Y	No
			400	4	24	06	08:00	Y	24	06	09:30	6.84	2.87	Y	N	No
5	55	108	1200	1	02	03	06:00	N	02	03	15:00	DI 13.38	4.63	N	N	Yes
			1200	2	24	04	07:00	N	24	04	12:15	↑ 13.69	4.63	N	N	No
			1200	3	03	06	06:00	N	03	06	09:30	↑ 14.91	4.63	N	N	Yes
			1200	4	26	06	08:00	N	26	06	11:30	↑ 16.78	4.63	N	N	Yes

LEGEND:
Y = YES – compliant with criterion N = NO – incompliant with criterion
DI = DRUG INTERACTION (raises concentration ↑ : lowers concentration ↓)

THERAPEUTIC DRUG MONITORING (2009)
(R.A. BRIDGENS)

Patient's Study No	Age	Wt kg	Daily Dose mg	Visit	Last Dose			Compliant Visits	Blood Sample			Carbamazepine Concentration				Fits
					Day	Month	Time Taken		Day	Month	Time Drawn	Measured µg/ml	Expected µg/ml	Measured Within Range	Compliant Concentration	
6	44	104	1600	1	09	03	20:00	Y	10	03		DI 12.12	6.41	N	N	No
			1600	2	07	04	06:15	Y	07	04	15:15	↑ 7.43	6.41	Y	Y	No
			1600	3	04	05	08:00	Y	04	05	09:10	8.44	6.41	Y	Y	No
			1600	4	29	06	20:00	N	30	06	10:45	5.59	6.41	Y	Y	No
7	29	88	400	1	26	03		Y	26	03		DI 4.35	1.89	Y	N	No
			400	2	28	04	08:00	Y	28	04	11:30	↑ 7.28	1.89	Y	N	Yes
			400	3	27	05	09:00	Y	27	05	09:30	4.94	1.89	Y	N	Yes
			400	4	18	06	07:00	N	18	06	11:15	6.36	1.89	Y	N	No
8	23	60	1200	1	16	03		Y	16	03		<0.50	8.33	N	N	No
			1200	2	09	04		N	09	04	08:45	4.82	8.33	Y	N	No
			1200	3	10	05	14:00	Y	11	05	09:20	<0.50	8.33	N	N	No
			1200	4	09	06	19:00	Y	10	06	07:05	1.45	8.33	N	N	No
9	61	95	400	1	18	03	14:00	Y	19	03		DI 2.94	1.75	N	Y	Yes
			400	2	15	04	14:00	Y	16	04	11:00	↑ 3.56	1.75	N	Y	No
			400	3	14	05	07:00	Y	14	05	12:00	3.82	1.75	N	Y	No
			400	4	11	06	08:00	Y	11	06	11:05	5.41	1.75	Y	Y	No
10	17	74	1000	1	07	04	19:00	Y	08	04	13:30	4.45	5.63	Y	Y	No
			1000	2	05	05	06:30	Y	05	05	09:25	9.10	5.63	Y	N	Yes
			1000	3	01	06	06:30	Y	01	06	09:00	8.40	5.63	Y	N	No
11	56	83	1200	1	11	03	-------	Y	11	03	08:50	3.55	6.02	N	N	No
			400	2	08	04	06:00	Y	08	04	09:30	0.58	2.01	N	N	No
			400	3	06	05	07:00	Y	06	05	09:15	<0.50	2.01	N	N	No
			400	4	04	06		Y	04	06		<0.50	2.01	N	N	No
12	38	80	800	1	11	03	07:00	Y	11	03		DI 9.14	4.17	Y	N	No
			800	2	05	04	19:00	N	06	05	14:50	↑ 9.07	4.17	Y	N	No
			800	3	03	05	07:00	Y	03	06	13:15	8.77	4.17	Y	N	No
			800	4	01	06	14:00	Y	01	07	14:35	7.89	4.17	Y	N	No

LEGEND:
Y = YES – compliant with criterion N = NO – incompliant with criterion
DI = DRUG INTERACTION (raises concentration ↑ : lowers concentration ↓)

THERAPEUTIC DRUG MONITORING (2009)
(R.A. BRIDGENS)

Patient's Study No	Age	Wt kg	Daily Dose mg	Visit	Last Dose			Compliant Visits	Blood Sample			Carbamazepine Concentration				Fits
					Day	Month	Time Taken		Day	Month	Time Drawn	Measured µg/ml	Expected µg/ml	Measured Within Range	Compliant Concentration	
13	29	71	800	1	09	03	08:00	Y	09	03		DI 4.16	4.69	Y	Y	Yes
			800	2	31	03	07:30	N	31	03	10:35	↓ 4.87	4.69	Y	Y	Yes
			800	3	29	04	07:00	Y	29	04	08:15	↓ 2.66	4.69	N	Y	No
			800	4	02	06	07:00	N	02	06	12:15	5.61	4.69	Y	Y	No
14	55	65	400	1	09	03	08:00	Y	09	03		DI 2.08	2.56	N	Y	No
				2	20	04	07:00	N	20	04		↓ <0.50	0.00	N		No
				3	18	05	06:00	Y	18	05	09:15	↓ 1.16	0.00	N		No
				4	15	06	06:00	Y	15	06	08:45	<0.50	0.00	N		No
15	31	100	1400	1	11	03	06:00	Y	11	03		DI 11.87	5.83	Y	N	No
			1400	2	08	04	06:00	Y	08	04	12:55	↑ 14.25	5.83	N	N	No
			600	3	02	06	20:00	N	02	06		↑ 12.33	2.50	N	N	No
				4	10	08		N								No
16	37	95	1200	1	16	03	20:00	Y	17	03		DI 9.63	5.26	Y	N	No
			1200	2	13	04	20:00	Y	14	04		↑	5.26			No
			1200	3	11	05	20:00	Y	12	05	13:35	↑ 7.12	5.26	Y	Y	No
			1200	4	08	06	20:00	Y	09	06	09:50	5.45	5.26	Y	Y	No
17	38	70	800	1	08	04	08:00	Y	08	04	12:00	10.00	4.76	Y	N	No
			800	2	06	05	08:00	Y	06	05	14:40	13.47	4.76	N	N	No
			400	3	29	06	20:00	N	01	07	13:45	11.48	2.38	Y	N	No
18	56	75	600	1	30	03	08:00	Y	30	03	11:00	4.11	3.33	Y	Y	No
			600	2	03	05	07:00	N	03	05	09:20	<0.50	3.33	N	N	No
				3	01	06	05:00	Y	01	06	11:45	1.33		N		No
				4	25	06		N								No
19	52	62	800	1	09	03		Y	10	03		DI 4.32	5.38	Y	N	No
			800	2	31	03	07:30	N	31	03	14:10	↑ 8.53	5.38	Y	N	No
			800	3	28	04	08:20	Y	28	04	09:15	↑ 11.11	5.38	Y	N	No
			800	4	26	05	10:00	Y	26	05	11:50	10.00	5.38	Y	N	Yes

LEGEND:
Y = YES – compliant with criterion N = NO – incompliant with criterion
DI = DRUG INTERACTION (raises concentration ↑ : lowers concentration ↓)

THERAPEUTIC DRUG MONITORING (2009)
(R.A. BRIDGENS)

Patient's Study No	Age	Wt kg	Daily Dose mg	Visit	Last Dose			Compliant Visits	Blood Sample			Carbamazepine Concentration				Fits
					Day	Month	Time Taken		Day	Month	Time Drawn	Measured µg/ml	Expected µg/ml	Measured Within Range	Compliant Concentration	
20	55	51	800	1	11	03	05:00	Y	11	03		DI 4.49	6.54	Y	Y	No
			800	2	08	04	07:00	Y	08	04	12:30	↓ 8.87	6.54	Y	N	No
			800	3	13	05	06:00	N	13	05	09:05	↓ 3.47	6.54	N	N	No
			800	4	10	06	08:00	Y	10	06	10:10	↓ 6.01	5.95	Y	Y	No
21	45	94	800	1	09	03	08:30	Y	09	03		10.37	3.55	Y	N	Yes
			800	2	31	03	08:00	N	31	03	08:45	8.15	3.55	Y	N	No
			800	3	27	05	06:00	N	27	05	10:35	8.15	3.55	Y	N	No
			800	4	23	06	06:00	Y	23	06	11:15	8.46	3.55	Y	N	No
22	43	50	800	1	19	03		Y	19	03		DI 6.70	6.67	Y	Y	No
			800	2	16	04	06:00	Y	16	04	10:05	↑ 8.46	6.67	Y	Y	No
			800	3	14	05	06:00	Y	14	05	08:45	↑ 9.20	6.67	Y	N	No
			800	4	11	06	06:00	Y	11	06	13:25	↑ 12.50	6.67	N	N	No
23	30	73	1600	1	06	03	07:00	Y	06	03		13.34	9.13	N	N	No
			1600	2	01	04	06:45	N	01	04	11:00	14.43	9.13	N	N	Yes
			1600	3	27	05	07:15	N	27	05	12:05	16.66	9.13	N	N	Yes
			1600	4	24	06	08:30	Y	24	06	13:35	18.18	9.13	N	N	No
24	32	96	800	1	31	03	08:00	Y	31	03	11:45	DI 7.28	3.47	Y	N	Yes
			800	2	25	05	20:00	N	26	05	12:35	↑ 7.25	3.47	Y	N	No
			800	3	30	06	08:00	N	30	06	12:00	↑ 6.84	3.47	Y	N	No
25	23	85	600	1	20	04		Y				DI	2.94			No
			600	2	18	06	08:30	N	18	06	14:30	↑ 6.66	2.94	Y	N	Yes
26	29	44	1600	1	18	03		Y	18	03	11:55	DI	15.15			Yes
			1600	2	14	04		Y	14	04	14:30	↓ 10.37	15.15	Y	Y	Yes
27	49	75	1600	1	11	03	06:00	Y	11	03	8.:45	11.55	8.89	Y	N	No
			1600	2	08	04	06:00	Y	08	04	11:20	<0.50	0.50	N	Y	No
			1600	3	03	06	06:00	N	03	06	11:25	<0.50	3.33	N	N	No

LEGEND:
Y = YES – compliant with criterion N = NO – incompliant with criterion
DI = DRUG INTERACTION (raises concentration ↑ : lowers concentration ↓)

THERAPEUTIC DRUG MONITORING (2009)
(R.A. BRIDGENS)

Patient's Study No	Age	Wt kg	Daily Dose mg	Visit	Last Dose			Compliant Visits	Blood Sample			Carbamazepine Concentration				Fits
					Day	Month	Time Taken		Day	Month	Time Drawn	Measured µg/ml	Expected µg/ml	Measured Within Range	Compliant Concentration	
28	35	60	400	1	08	03		Y	08	03		DI 6.34	5.56	Y	Y	No
				2	20	04	08:00	N	20	04	09:25	↑ <0.50		N		No
				3	13	05	06:00	N	13	05	13:25	6.75		Y		No
29	49	53	800	1	06	04	07:00	Y	06	04	10:45	6.07	6.29	Y	Y	No
			800	2	25	05	06:00	N	25	05	09:00	2.07	6.29	N	N	No
			800	3	25	06		Y	25	06						No
30	45	55	800	1	10	03	07:30	Y	10	03		<0.50	6.06	N	N	No
			800	2	07	04	08:08	N	07	04	09:30	1.78	6.06	N	N	Yes
			800	3	02	06		N	02	06		8.35	6.06	Y	Y	No
31	33	90	1600	1	04	03	08:00	Y	04	03		DI	7.41			No
			1600	2	12	05	20:00	N	13	05	09:00	↓ 6.04	7.41	Y	Y	No
			1600	3	10	06	06:00	Y	10	06	09:30	8.08	7.41	Y	Y	No
32	45	70	600	1	23	03		Y	23	03		5.25	3.57	Y	Y	No
			600	2	20	04	07:00	Y	20	04	11:00	6.73	3.57	Y	Y	No
			600	3	19	05	06:00	Y	19	05	09:00	6.23	3.57	Y	Y	No
33	23	70	1200	1	21	04	07:00	Y	21	04	15:00	DI 6.02	7.14	Y	Y	No
			1200	2	14	05	07:00	N	14	05	10:00	↓ 2.80	7.14	N	N	No
			1200	3	10	06	07:30	Y	10	06	14:20	6.69	7.14	Y	Y	No
34	34	70	400	1	04	02	07:30	N	04	02	15:00	6.96	2.38	Y	N	Yes
			400	2	29	04	19:00	N	30	04	14:00	1.86	2.38	N	N	Yes
			400	3	15	06	10:00	N	15	06	11:40	3.74	2.38	N	Y	No
35	57	88	400	1	29	04	08:00	Y	29	04	09:30	5.03	1.89	Y	N	Yes
			400	2	28	05	06:00	Y	28	05	14:00	4.55	1.89	Y	N	Yes
36	16	60	600	1	05	02	06:00	N	05	02		10.20	4.17	Y	N	No
			1800	2	09	03	06:00	N	09	03			12.50			No
			400	3	05	05	06:00	N	05	05	15:05	4.55	2.78	Y	N	No
37	43	68	400	1	14	04	19:00	Y	15	04	14:35	<0.50	2.45	N	N	No
			400	2	12	05	07:00	Y	12	05	10:00	6.87	2.45	Y	N	No
			400	3	10	06		Y	10	06	11:00	6.30	2.45	Y	N	No

LEGEND:
Y = YES – compliant with criterion N = NO – incompliant with criterion
DI = DRUG INTERACTION (raises concentration ↑ : lowers concentration ↓)

THERAPEUTIC DRUG MONITORING (2009)
(R.A. BRIDGENS)

Patient's Study No	Age	Wt kg	Daily Dose mg	Visit	Last Dose			Compliant Visits	Blood Sample			Carbamazepine Concentration				Fits
					Day	Month	Time Taken		Day	Month	Time Drawn	Measured µg/ml	Expected µg/ml	Measured Within Range	Compliant Concentration	
38	33	60	800	1	20	04	08:40	Y	20	04	14:00	DI 8.84	5.56	Y	N	Yes
			800	2	12	05	07:00	N	12	05		↓ 3.76	5.56	N	Y	No
			800	3	09	06	07:00	Y	09	06	11:05	↓ <0.50	5.56	N	N	No
39	34	53	400	1	06	03	05:00	N	06	03		DI 8.52	3.14	Y	N	No
			400	2	01	04	07:00	N	01	04	09:45	↑ 8.26	3.14	Y	N	No
			400	3	26	05	20:00	N	27	05	09:35	↑ 8.76	3.14	Y	N	No
40	30	75	1200	1	06	03	07:00	Y	06	03	14:05	13.95	6.67	N	N	No
			1200	2	29	04	07:00	N	29	04	10:15	14.71	6.67	N	N	No
			1200	3	24	06	07:00	N	24	06	11:55	12.21	6.67	N	N	No
41	65	80	1000	1	25	05	08:00	Y	25	05	09:10	DI 11.08	5.21	Y	N	Yes
			1400	2	10	06	08:00	N	10	06	08:45	↑ 1.45	7.29	N	N	Yes
			1400	3	24	06	08:00	N	24	06	11:40	↑ 12.51	7.29	N	N	No
42	66	72	400	1	18	03		Y	18	03		<0.50	2.31	N	N	Yes
			400	2	15	04	07:00	Y	15	04	13:20	<0.50	2.31	N	N	Yes
43	55	48	400	1	05	03	06:00	Y	05	03		DI <0.50	3.47	N	N	No
			400	2	05	04	06:00	Y	05	04	13:30	↓ <0.50	3.47	N	N	Yes
44	55	64	400	1	24	03	07:00	N	24	03	13:45	1.07	2.60	N	Y	Yes
			400	2	07	04	06:00	N	27	04	13:15	8.10	2.60	Y	N	No
45	35	58	800	1	19	03		Y	19	03		7.24	5.75	Y	Y	No
				2	16	04	06:00	Y	16	04	15:00	7.36	5.75	Y	Y	No
46	29	84	800	1	03	03	07:00	Y	03	03		3.24	3.97	N	Y	No
			800	2	07	04	08:00	N	07	04	12:00	3.06	3.92	N	Y	No
47	49	64	1600	1	06	03		Y	06	03		<0.50	10.42	N	N	Yes
			1600	2	01	04		N	01	04	08:00	<0.50	10.42	N	N	Yes
48	60	75	800	1	13	04	09:00	Y	13	04	10:30	3.92	4.44	N	Y	No
			800	2	12	05	06:00	Y	12	05	10:30	1.10	4.44	N	N	Yes
49	19	68	800	1	09	03	06:30	Y	09	03		DI 5.18	4.90	Y	Y	No
			800	2	07	04	07:30	Y	07	04	08:30	↑ 9.09	4.90	Y	N	No

LEGEND:

Y = YES – compliant with criterion N = NO – incompliant with criterion

DI = DRUG INTERACTION (raises concentration ↑ : lowers concentration ↓)

THERAPEUTIC DRUG MONITORING (2009)
(R.A. BRIDGENS)

Patient's Study No	Age	Wt kg	Daily Dose mg	Visit	Last Dose			Compliant Visits	Blood Sample			Carbamazepine Concentration				Fits
					Day	Month	Time Taken		Day	Month	Time Drawn	Measured µg/ml	Expected µg/ml	Measured Within Range	Compliant Concentration	
50		45	400	1	30	03	08:00	Y	30	03	12:30	1.53	3.70	N	Y	No
			400	2				N			08:00	3.11	3.70	N	Y	Yes
51	33	65	400	1	03	03	08:00	Y	03	03		10.63	2.56	Y	N	Yes
			400	2	31	03	07:45	Y	31	03	13:45	6.96	2.56	Y	N	No
52	38	75	1400	1	18	03	06:00	Y	18	03	09:00	6.43	7.78	Y	Y	No
			1400	2	13	05	06:30	N	13	05	09:40	13.81	7.78	N	N	No
53	41	72	400	1	27	03	07:00	Y	27	03		3.68	2.31	N	Y	No
			400	2	30	04	06:30	Y	30	04	11:00	5.22	2.31	Y	N	No
54	48	64	800	1	11	05		Y	11	05	16:00		5.21			No
			800	2	09	06	08:45	Y	09	06	11:05	3.36	5.21	N	N	Yes
55	66	59	1000	1	05	05	07:00	Y	05	05	15:05	8.74	7.06	Y	N	No
56	58	69	800	1	25	03	06:00	Y	25	03		8.65	4.83	Y	N	No
			800	2	19	05	09:00	N	19	05	09:50	10.32	4.93	Y	N	No
57	56		600	1	11	03	07:30	Y	11	03		7.53	4.46	Y	N	No
58	28	56	1200	1	11	03		Y	11	03		5.35	8.93	Y	N	No
			1200	2	01	07	07:00	N	01	07	10:15	5.89	8.93	Y	Y	No
59	42	84	800	1	01	04	08:00	Y	01	04	10:15	8.01	3.97	Y	N	No
			800	2	26	05	20:00	N	27	05	11:40	7.32	3.97	Y	N	No
60	28	65	800	1	15	04	06:00	Y	15	04	14:40	7.36	5.13	Y	N	No
			800	2	22	05	06:00	N	22	05	11:05	10.09	5.13	Y	N	No
61	42	60	800	1	09	03	18:00	Y	10	03	08:00	<0.50	5.56	N	N	No
			800	2	28	04	08:00	N	28	04	11:00	<0.50	5.56	N	N	No
62		64		1	24	03	07:00	Y	24	03		1.07		N		No
63	24	59		1	11	03	06:00	Y	11	03		5.47		Y		No
64	52	80		1	23	03	07:00	Y	23	03	12:00	5.92		Y		No
65	45	75	1200	1	12	03	19:00	Y	13	03		5.56	6.67	Y	Y	No

LEGEND:

Y = YES – compliant with criterion N = NO – incompliant with criterion

DI = DRUG INTERACTION (raises concentration ↑ : lowers concentration ↓)

THERAPEUTIC DRUG MONITORING (2009)
(R.A. BRIDGENS)

Patient's Study No	Age	Wt kg	Daily Dose mg	Visit	Last Dose			Compliant Visits	Blood Sample			Carbamazepine Concentration				Fits
					Day	Month	Time Taken		Day	Month	Time Drawn	Measured µg/ml	Expected µg/ml	Measured Within Range	Compliant Concentration	
66	51	70	800	1	12	06	08:00	Y	12	06	13:05	3.48	4.76	N	Y	No
67	58	117	400	1	30	03	07:30	Y	30	03	11:40	3.82	1.42	N	N	No
68	43	89	1200	1	30	03	20:00	Y	31	03		5.03	5.62	Y	Y	Yes
69	24	70		1	16	03	07:00	Y	16	03		7.98		Y		No
70	68	65	200	1	20	03		Y	20	03		1.31	1.28	N	Y	No
71	43	80		1	25	03	14:00	Y	25	03	16:00	DI ↑ 7.97	3.60	Y		No
72	36	75		1	09	03	06:00	Y	09	03		4.03		Y		No
73	60	81	800	1	01	06	21:00	Y	02	06	08:00		4.12			No
74		89		1	29	06	20:00	Y	30	06	10:45	<0.50		N	N	No
75	49	72		1	25	03	08:30	Y	25	03		6.22		Y	N	No
76	55	58		1	05	03		Y	05	03		13.91		N		No
77	60			1	08	04		Y	08	04		<0.50		N	N	No
78	27	72	800	1	06	03	08:00	Y	06	03	09:30	4.16	4.63	Y	Y	No

LEGEND:

Y = YES – compliant with criterion N = NO – incompliant with criterion

DI = DRUG INTERACTION (raises concentration ↑ : lowers concentration ↓)