A limited sampling method for the estimation of AUC and $C_{\max}$ of carbamazepine and carbamazepine epoxide following a single and multiple dose of a sustained-release product

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Aims The objectives of this study are to develop a model to predict area under the curve (AUC) and maximum plasma concentration ($C_{\max}$) of carbamazepine (CBZ) and its active metabolite carbamazepine epoxide (CBZE) following single and multiple dose of CBZ using one or two samples in volunteers.

Methods Limited sampling models (LSM) were developed for CBZ and CBZE following 200–800 mg single oral dose and 400–800 mg twice daily dose for 14 days of a sustained-release product (CBZ-SR) to estimate AUC and $C_{\max}$. The LSM was developed from a training data set of 15 subjects using one blood sample taken at 48 h following a single dose. The model was validated on 60 subjects who received different doses of CBZ. Following multiple dosing, the LSM was developed from a training data set of 10 subjects using the steady state $C_{\min}$ (plasma concentration obtained 5 min before the last CBZ-SR dose).

Results The model provided good estimates of AUC and $C_{\max}$ for CBZ and CBZE. The bias and the precision of the predicted AUC and $C_{\max}$ for CBZ and CBZE were less than 10% and 15%, respectively. Similar results were obtained when CBZ was given as multiple dose.

Conclusions The method described here may be used to estimate AUC and $C_{\max}$ for CBZ and CBZE without detailed pharmacokinetic studies following single or multiple dose of CBZ.

Keywords: carbamazepine, limited sampling, prediction of AUC and $C_{\max}$

Introduction

Carbamazepine (CBZ) is an anticonvulsant drug which is widely used in the treatment of epilepsy [1]. It is also a specific analgesic for trigeminal neuralgia [1]. Usual adult therapeutic levels are between 4 and 12 $\mu\text{g ml}^{-1}$ [1]. Pharmacokinetic studies of CBZ indicate that the peak plasma levels of carbamazepine are highly variable, with peak plasma levels reaching between 4 to 8 h (peak plasma levels may occur as late as 24 to 26 h) [2]. The absolute bioavailability is >70% [3]. The apparent volume of distribution is $1.4 \pm 0.4 \text{ l kg}^{-1}$ [3]. Carbamazepine is 70–80% bound to plasma proteins [1]. Carbamazepine is metabolized in the liver and less than 1% of the dose is excreted unchanged in urine [3]. Since carbamazepine induces its own metabolism, the half-life is also variable [2]. Initial half-life values following a single dose range from 18–55 h and 5–26 h on repeated dosing [2]. The apparent oral clearance following a single dose was $25 \pm 5 \text{ ml min}^{-1}$ and $80 \pm 30 \text{ ml min}^{-1}$ following multiple dosing [2].

One of the major metabolites of CBZ is CBZ-10–11-epoxide (CBZE). CBZE has an anticonvulsant activity comparable with that of the parent compound in animal models of epilepsy [4]. Following a single 100 mg oral dose of CBZE enteric coated capsule, the $t_{\max}$ and $C_{\max}$ of CBZE were $6.7 \pm 3 \text{ h}$ and $1.1 \pm 0.3 \mu\text{g ml}^{-1}$, respectively [4]. The volume of distribution (V/F) was $1.1 \pm 0.2 \text{ l kg}^{-1}$ [5]. The plasma half-life for CBZ epoxide was $7.4 \pm 1.8 \text{ h}$, whereas clearance was $1.7 \pm 0.3 \text{ ml min}^{-1} \text{ kg}^{-1}$ [4]. CBZ-10–11-epoxide is 50% bound to plasma proteins [3].

Pharmacokinetic parameters such as area under the curve (AUC) and maximum plasma concentration ($C_{\max}$) may vary considerably among patients, depending on factors like age, race, and gender. Both AUC and $C_{\max}$ are indices of exposure of a patient to a given drug. In order to accurately measure AUC and $C_{\max}$ multiple blood samples are required. However, frequent blood sampling from patients is time-consuming and expensive. One approach to this problem is to use a limited-sampling strategy. Two methods are widely used to estimate pharmacokinetic parameters from a limited number of samples:

(i) The optimal-sampling theory which has been described in detail by Schumacher [5] and Drusano *et al.* [6].

(ii) The limited-sampling model (LSM) is simpler and requires only one to three samples. LSM has been used by

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many investigators to predict the AUC of anticancer drugs [7–10]. Limitations of LSM have been described by Warmerdam *et al.* [11].

This study describes a LSM approach to estimating the AUC and $C_{\max}$ of CBZ and CBZE following single and multiple dosing of a sustained-release product of carbamazepine (CBZ-SR). The objectives of this study were as follows:

(i) To develop a model to predict AUC and $C_{\max}$ of CBZ and CBZE following a single dose of CBZ using one or two samples in volunteers.

(ii) To develop a model to predict AUC and $C_{\max}$ of CBZ and CBZE following multiple doses of CBZ using one or two samples in the volunteers.

The current approach is distinct from the work done with anticancer drugs [7–10] for the following reasons:

(i) The LSM predicts not only the AUC but also $C_{\max}$.

(ii) The LSM also predicts the AUC and $C_{\max}$ of CBZE an active metabolite of CBZ, and;

(iii) The LSM has been developed to predict AUC and $C_{\max}$ of both CBZ and CBZE following multiple dosing.

Methods

Pharmacokinetic studies

Pharmacokinetic studies were designed and conducted by the investigators of Pharmavene Inc. [12], to evaluate: (i) bioequivalence of to be marketed formulation and clinical trial capsule following oral administration of CBZ-SR, (ii) dose proportionality (200, 300, 400, 500, 600 and 800 mg dose), (iii) effect of food on the pharmacokinetics of CBZ-SR, and, (iv) multiple dose study (CBZ-SR given every 12 h for 14 days).

Single dose

The LSM was developed from dose proportionality and a preliminary pharmacokinetic study. The dose proportionality study was designed as an outpatient, open-label, randomized, fasting, six-way crossover study. Twelve healthy male subjects entered the study. The volunteers received single oral doses of 200, 300, 400, 500, 600, and 800 mg CBZ-SR. The washout period between each dose was 14 days. Blood samples were collected at the following time points on the day of each drug administration: 0 (pre-dose), and, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 29, 34, 39, 48, 72, 96, 168, and 216 h post-dose. The blood samples were immediately centrifuged, and plasma stored at approximately -20°C . The concentrations of carbamazepine and carbamazepine-10,11-epoxide were determined using high pressure liquid chromatography with ultraviolet detection. The limit of detection for carbamazepine and carbamazepine-10,11-epoxide was 0.02 to $10\text{ }\mu\text{g ml}^{-1}$ and 0.01 to $1.0\text{ }\mu\text{g ml}^{-1}$, respectively. The between-assay precision was less than 10% for all CBZ and CBZE quality control samples. The between-assay accuracy ranged from 105.8–112.7% and 103.6–107.7% for the CBZ and CBZE quality control samples, respectively.

Three different subjects from the 200, 300, 600, and 800 mg doses and three subjects from preliminary pharmacokinetic study were selected randomly for model development

($n=15$, training data set). The model was validated in 60 subjects, i.e. nine subjects from dose proportionality study and 51 subjects from different pharmacokinetic studies (as mentioned under pharmacokinetic studies). The AUC from zero to infinity was calculated by the trapezoidal rule and $C_{\max}$ was the highest concentration observed on the plasma concentration *vs* time curve.

Development of the model (single dose)

The LSM was developed using the training data set ($n=15$). The correlation between CBZ concentrations ($\mu\text{g ml}^{-1}$, independent variable) of varying doses (in mg) at a selected time point *vs* the AUC ($0, \infty$) ($\mu\text{g ml}^{-1}\text{ h}$, dependent variable) was evaluated by multiple regression analysis on the training data set. The linear regression equation which gave the best correlation coefficient (r) for a single sampling time *vs* AUC was chosen as the LSM model. To develop the model to predict $C_{\max}$ ($\mu\text{g ml}^{-1}$), the values of $C_{\max}$ of varying doses of CBZ from the same 15 subjects (as of AUC) were plotted as a dependent variable *vs* concentration as the independent variable.

Good correlations were found between the AUC and CBZ plasma concentrations and between the $C_{\max}$ and CBZ plasma concentrations at 12, 24 and 48 h. The best correlations ($r=0.985$) for AUC was found at 48 h and the best correlation ($r=0.994$) for $C_{\max}$ was observed at 24 h after CBZ administration. At 48 h the correlation between CBZ plasma concentrations and $C_{\max}$ was 0.967. Since the objective of the LSM is to use the minimum number of plasma samples, for practical purposes it was decided that plasma concentration obtained at 48 h following CBZ-SR administration will be appropriate for the prediction of both AUC and $C_{\max}$ of CBZ. Therefore, the predicted AUCs and $C_{\max}$ s of CBZ were estimated from the equation based on CBZ concentrations measured at 48 h in the validation data set.

$$\text{AUC}_{(\text{predicted})} = 98.9 \times C_{48\text{h}} + 10.3 + 0.0123 \text{ CBZ dose} \quad (1)$$

$$C_{\max} (\text{predicted}) = 0.92 \times C_{48\text{h}} + 0.35 + 0.0019 \text{ CBZ dose} \quad (2)$$

The LSM to predict AUC and $C_{\max}$ for CBZE was developed using 48 h plasma concentration of CBZE following CBZ-SR administration. Good correlations were found between the AUC and CBZ plasma concentrations ($r=0.980$) and between the $C_{\max}$ and CBZ plasma concentrations ($r=0.988$) at 48 h. Therefore, the predicted AUCs and $C_{\max}$ s of CBZE were estimated from the equation based on CBZE concentrations measured at 48 h in the validation data set.

$$\text{AUC}_{(\text{predicted})} = 0.065 \times C_{48\text{h}} + 2.2 + 0.0037 \text{ CBZ dose} \quad (3)$$

$$C_{\max} (\text{predicted}) = 1.0 \times C_{48\text{h}} - 1.6 + 0.053 \text{ CBZ dose} \quad (4)$$

It should be noted that the plasma concentrations of CBZE are in ng ml^{-1} . The units for AUC and $C_{\max}$ are in $\mu\text{g ml}^{-1}\text{ h}$ and ng ml^{-1} , respectively.

Validation of the model

For model validation, the predicted AUCs and $C_{\max}$ s were correlated with the observed AUCs and $C_{\max}$ s in 60 subjects who received different doses of CBZ. Since the dose proportional study was a crossover study, the same subjects received different doses of CBZ-SR, therefore overall 104 plasma concentrations of CBZ and CBZE from 60 subjects were used to validate the LSM.

Development of the model (multiple dose)

In the multiple dose study, 24 patients with epilepsy received CBZ-SR every 12 h (morning and evening) for 14 days. The daily dose administered to each patient was either 800, 1200, or 1600 mg of CBZ-SR. On day 14, blood samples were collected 5 min before drug administration and hourly for 24 h after administration.

The LSM was developed using the training data set ($n = 10$). The correlation between CBZ concentration (independent variable) of varying doses at time zero or just before the administration (5 min) of the last dose of CBZ *vs* the AUC (0, 12 h) and $C_{\max}$ (dependent variable) was evaluated by multiple regression analysis on the training data set. The correlation between the AUC (0, 12 h) and CBZ plasma concentrations and between the $C_{\max}$ and CBZ plasma concentrations at time zero was 0.967 and 0.923, respectively.

The LSM for CBZE was developed as described above. The correlation between the AUC (0, 12 h) and CBZE plasma concentrations and between the $C_{\max}$ and CBZE plasma concentrations at time zero was 0.994 and 0.968, respectively. The following equations were used for the model validation:

CBZ

$$\text{AUC}_{(\text{predicted})} = 11.8 \times C_0 + 10.6 + 0.0059 \text{ CBZ dose} \quad (5)$$

$$C_{\max} (\text{predicted}) = 1.05 \times C_0 + 1.4 + 0.0008 \text{ CBZ dose} \quad (6)$$

CBZE

$$\text{AUC}_{(\text{predicted})} = 11.7 \times C_0 - 1.4 + 0.0082 \text{ CBZ dose} \quad (7)$$

$$C_{\max} (\text{predicted}) = 1.0 \times C_0 - 0.05 + 0.001 \text{ CBZ dose} \quad (8)$$

Plasma concentrations of CBZE are in $\mu\text{g ml}^{-1}$. The units for AUC and $C_{\max}$ are in $\mu\text{g ml}^{-1} \text{ h}$ and $\mu\text{g ml}^{-1}$, respectively.

Validation of the model

The multiple-dose model was validated on 14 patients who received different doses of CBZ-SR.

Statistical analysis

The bias of the models was estimated by calculating the mean prediction error (MPE). The precision of the model was measured by calculating mean absolute error (MAE)

and the root mean square prediction error (RMSE) according to the following equations [13]:

$$\text{MPE} = \frac{\text{Sum (predicted—observed)}}{n}$$

$$\text{MAE} = \frac{\text{Sum |predicted—observed|}}{n}$$

$$\text{Mean Square Error (MSE)} = \frac{\text{Sum (predicted—observed)}^2}{n}$$

$$\text{RMSE} = (\text{MSE})^{1/2}$$

Results

Single dose

CBZ Figure 1 shows the mean plasma concentration *vs* time plot of CBZ and CBZE following a single 500 mg oral dose of CBZ-SR. The figure indicates that time to reach maximum plasma concentration for CBZ and CBZE is 25 h and 38 h, respectively. Table 1 represents the best correlation coefficient obtained for AUC or $C_{\max}$ *vs* CBZ plasma concentrations at different time points for the model development. The LSM developed from one sample (48 h plasma concentration, $r = 0.985$) to predict AUC gave good prediction across all doses (200–800 mg). The model was used to predict AUC in 60 subjects (104 total observations) who received 200–800 mg doses of CBZ under fasting conditions (Table 2). The precision of the estimated AUC was excellent with no bias. There were 95 observations in which the difference between the predicted and the observed AUC values was less than $40 \mu\text{g ml}^{-1} \text{ h}$ (15% of the mean observed AUC). The highest difference between the predicted and the observed AUC was $70 \mu\text{g ml}^{-1} \text{ h}$ (26% of the mean AUC).

The best correlation coefficient ($r = 0.994$) obtained for $C_{\max}$ *vs* CBZ plasma concentrations at different time points was at 24 h (Table 1). At 48 h the correlation coefficient was 0.967 and it was felt that the 48 h CBZ plasma concentrations are appropriate for the prediction of both AUC and $C_{\max}$ as the $t_{\max}$ for CBZ-SR was slightly over 30 h. Therefore, the 48 h plasma concentrations were used to develop the LSM to predict $C_{\max}$. The LSM provided good estimates for $C_{\max}$ across all doses of CBZ (Table 2) with good precision and without bias. There were 83 observations in which the difference between the predicted and the observed $C_{\max}$ were less than $0.50 \mu\text{g ml}^{-1}$ (15% of the mean observed $C_{\max}$). The highest difference between the predicted and the observed $C_{\max}$ was $1.52 \mu\text{g ml}^{-1}$ (43% of the mean $C_{\max}$).

CBZE The LSM developed from one sample (48 h plasma concentration, $r = 0.980$) to predict AUC of CBZE gave good estimation of AUC following CBZ administration (Table 2). There were 90 observations in which the difference between the predicted and the observed AUC values were less than $2.9 \mu\text{g ml}^{-1} \text{ h}$ (15% of the mean observed AUC). The highest difference between the predicted and the observed AUC was $9.9 \mu\text{g ml}^{-1} \text{ h}$ (51% of the mean AUC). The next highest difference between

Figure 1 Mean ($\pm$ s.d.) plasma concentration of CBZ (●) and CBZE (○) following 500 mg CBZ-SR dose to 12 healthy volunteers.

Table 1 Correlation between plasma concentration and AUC or $C_{\max}$ at different time points for the training data set.

Concentration	AUC Correlation coefficient	$C_{\max}$ Correlation coefficient
<i>Single dose</i>		
CBZ		
C_{12h}	0.918	0.983
C_{24h}	0.933	0.994
C_{48h}	0.985	0.967
CBZE		
C_{48h}	0.980	0.988
<i>Multiple dose</i>		
CBZ	0.962	0.775
1C_o	0.967 ²	0.923
CBZE		
1C_o	0.994	0.968

1 = 5 min before the administration of last CBZ dose.

2 = AUC (0, 12 h).

the predicted and the observed AUC was $4.9 \mu\text{g ml}^{-1} \text{ h}$ (25% of the mean AUC).

The predicted $C_{\max}$ was in good agreement with the observed $C_{\max}$ with no bias in the estimation. There were 84 observations in which the difference between the predicted and the observed $C_{\max}$ were less than 37 ng ml^{-1} (15% of the mean observed $C_{\max}$). The highest difference between the predicted and the observed $C_{\max}$ was 98 ng ml^{-1} (39% of the mean $C_{\max}$).

Multiple dose

CBZ Table 1 shows the correlation coefficient obtained for AUC (0, 12 h) or $C_{\max}$ vs CBZ plasma concentrations at time zero (5 min before the administration of last CBZ dose) following different doses of CBZ (400–800 mg every

Table 2 Predicted and observed AUC ($\mu\text{g ml}^{-1}$) and $C_{\max}$ of CBZ and CBZE following a single dose.

Group	CBZ		CBZE	
	AUC	$C_{\max}^1$	AUC	$C_{\max}^2$
<i>n</i>	104	104	104	104
Mean $\pm$ s.d. (LSM)	266 ± 95	3.6 ± 1.1	18.5 ± 8.0	247 ± 123
Range	105–578	1.6–7.1	8.1–46.1	88–670
Mean $\pm$ s.d. (observed)	267 ± 90	3.5 ± 1.2	19.3 ± 8.4	249 ± 120
Range	106–576	1.5–6.8	6.4–47.9	84–640
%MPE	0.20	1.2	4.2	0.60
%MAE	6.1	10.0	8.1	9.5
%RMSE	8.2	12.8	10.7	11.9

$C_{\max}^1 = \mu\text{g ml}^{-1}$.

$C_{\max}^2 = \text{ng ml}^{-1}$.

12 h for 14 days) for the model development. The model was used to predict AUC in 14 subjects who received 400–800 mg doses of CBZ twice daily for 14 days under fasting conditions (Table 3). The LSM developed from one sample

Table 3 Predicted and observed AUC (0, 12 h) ($\mu\text{g ml}^{-1} \text{ h}$) and $C_{\max}$ ($\mu\text{g ml}^{-1}$) of CBZ and CBZE following multiple dosing.

Group	CBZ		CBZE	
	AUC	$C_{\max}$	AUC	$C_{\max}$
<i>n</i>	14	14	14	14
Mean $\pm$ s.d. (LSM)	117 ± 31	11.0 ± 2.7	23.4 ± 7.5	2.2 ± 0.7
Range	79–182	7.5–16.8	12.7–37.0	1.3–3.5
Mean $\pm$ s.d. (observed)	114 ± 30	11.1 ± 2.7	22.6 ± 8.0	2.2 ± 0.8
Range	71–170	7.4–16.6	12.4–37.9	1.2–3.6
%MPE	3.0	0.60	3.1	2.3
%MAE	5.9	4.4	7.8	8.7
%RMSE	7.0	5.9	9.7	10.2

($r=0.967$) to predict AUC provided good estimation of AUC across all doses. The highest difference between the predicted and the observed AUC was $13.1 \mu\text{g ml}^{-1} \text{ h}$ (11% of the mean AUC).

The correlation coefficient obtained for C_{max} vs CBZ plasma concentrations at time zero was 0.923 (Table 1). A good precision with no bias was observed with the estimated C_{max} (Table 3). The highest difference between the predicted and the observed C_{max} was $1.5 \mu\text{g ml}^{-1}$ (14% of the mean C_{max}).

CBZE Table 1 shows the correlation coefficient obtained for AUC (0, 12 h) or C_{max} vs CBZE plasma concentrations at time zero following different doses of CBZ for the model development. The LSM developed from one sample to predict AUC and C_{max} of CBZE following multiple dosing provided good prediction across all doses. The highest difference between the predicted and the observed AUC and C_{max} was $4.0 \mu\text{g ml}^{-1} \text{ h}$ (18% of the mean AUC) and $0.43 \mu\text{g ml}^{-1}$ (20% of the mean C_{max}), respectively.

Discussion

Most of the antiepileptic drugs have narrow therapeutic ranges and both the therapeutic and toxic effects are related to plasma concentrations rather than dose [1]. As a result, antiepileptic drugs require constant monitoring of daily dosage and the dosing intervals to maintain the plasma concentrations within the desired levels [1]. The titration of antiepileptic drugs against the clinical effects may not produce desirable effects as the titration may delay the optimization of drug therapy [1]. This delay may result in sub-therapeutic or toxic effects. Therefore, a pharmacokinetic approach may be suitable for the dosage adjustment of antiepileptic drugs in a patient population.

Carbamazepine is one of those antiepileptic drugs which have a narrow therapeutic range ($4\text{--}12 \mu\text{g ml}^{-1}$). Its absorption is slow and erratic and there is considerable intra- and inter-individual variability in peak plasma concentrations, half-life and clearance. CBZ induces its own metabolism, which can lead to 3 fold increase in clearance over the first 3 to 5 weeks of therapy [1]. Since the extent of autoinduction is variable among patients, dosage requirements are also variable. Due to autoinduction, the maintenance dose of CBZ may need to be increased. Furthermore, autoinduction also leads to the formation of CBZE which is an active metabolite of CBZ and is believed to be equipotent in its effect to that of the parent drug [1]. Therefore, optimization of CBZ therapy in individual patients is highly desirable. A pharmacokinetic approach to link the therapeutic effect and toxicity of CBZ may lie in estimating the AUC and C_{max} , especially AUC which is an index of total exposure of a drug. In the past optimization methods for CBZ dosage regimen based on the population pharmacokinetics, least square method and the least square method based on the Bayesian algorithm have been attempted [14]. The Bayesian non-linear regression approach, produced clinically acceptable precision in terms of prediction of concentrations but required three or four data points for clinically acceptable prediction. Furthermore, this approach did not take CBZE into account and was only limited to CBZ concentrations.

This study indicates that a limited sampling model can be developed for CBZ and its active metabolite CBZE to predict AUC and C_{max} using one plasma concentration taken at 48 h following a single oral dose of CBZ-SR. This study also demonstrates that taking one blood sample just before the administration of a next dose of CBZ-SR (assuming steady state has been achieved), it is possible to predict both AUC and C_{max} of CBZ and CBZE following multiple dosing. Although the LSM has been used for anticancer drugs [7–10], this technique has not been used for antiepileptic drugs. Cooper and co-workers [15] were the first to investigate LSM for lithium which led to the utilization of this method in clinical settings. The LSM described here for CBZ-SR is distinct from other studies done with anticancer drugs. In this study, we not only predicted the AUC and C_{max} of parent compound but also its active metabolite from a blood sample taken at 48 h following a single dose. This study also describes how to predict the AUC and C_{max} of CBZ-SR and its metabolite following multiple dosing. Although, following multiple dosing the sample size for the validation data set was fairly small ($n=14$), we believe that the LSM approach is applicable for the prediction of AUC and C_{max} following multiple dosing of CBZ-SR. Recently, using a computer simulation study [16], it has been shown in a larger sample ($n=40$) that the proposed method works fairly well following multiple dosing.

The equations for the prediction of AUC and C_{max} described in this paper are useful for the same formulation and dose of CBZ-SR. Any change in the formulation or dose or incorporation of disease states e.g., renal or hepatic impairment will require different equations.

In the limited sampling approach, the selection of the time point (s) is very critical for the prediction of AUC and C_{max} . It is the experience of the authors that the best correlation between plasma concentration and AUC or C_{max} is generally obtained after the t_{max} or when the absorption is almost complete. In some subjects the t_{max} of CBZ was fairly long ($>30 \text{ h}$), therefore it is not surprising that in order to predict AUC ($0, \infty$) plasma samples at 48 h appeared to be appropriate. If one is willing to accept comparatively higher error in the prediction of AUC (without compromising the clinical efficacy of CBZ-SR when measured against AUC), then the prediction of AUC from plasma sample at 24 h may be suitable. However, in real life situation, CBZ will be given at 12 h intervals which will ultimately result in reaching the steady-state. Therefore, the prediction of AUC and C_{max} within the dosing interval can be easily made by taking a plasma sample just before the next dose, provided a steady state has been achieved.

It should be noted that the limited sampling approach does not necessarily mean that only one time point will be sufficient for the prediction of AUC and C_{max} . Two or three time points may be required for the accurate prediction of AUC and C_{max} of a drug. Despite the fact that CBZ is a highly variable drug, we managed to predict the AUC and C_{max} of both CBZ and CBZE using one sample. This may not be true with other antiepileptic drugs or other formulations of CBZ. In a separate study, it was found that the prediction of AUC and C_{max} of vigabatrin [17] was possible from only one sample, but flunarazine [18] a highly

variable antiepileptic drug required two time points for the prediction of the AUC and $C_{\max}$.

The LSM is valuable during clinical trials where either blood samples are not drawn or one or two samples taken randomly may not provide any true information relating to the efficacy and toxicity of a drug with plasma concentrations. Since AUC represents the total exposure of a drug, taking one or two blood samples at appropriate time (s), it will be possible to predict both AUC and $C_{\max}$ with sufficient accuracy to the efficacy or toxicity of a drug in a general population or in a particular subject. This method is also useful in children where extensive sampling is not possible. The long term advantage is that once the limited sampling method has been developed for a drug it can also be used in the clinical settings [15] or under any experimental setting without the need of extensive sampling. Our main objective in this study is to introduce a very simple and easy method using carbamazepine as a model drug to predict AUC and $C_{\max}$ not only for the parent compound but also its active metabolite and to convey the message to the pharmaceutical scientists/clinicians to use the method during the clinical trials or the clinical settings. Since the clinical trials are large in sample size, it is not possible to take frequent blood samples in patients. Hence the LSM can provide a tool to estimate AUC and $C_{\max}$ which then can be used to relate the toxicity or efficacy of a drug.

The views expressed in this article are those of the authors and do not reflect the official policy of the FDA. No official support or endorsement by the FDA is intended or should be inferred.

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