Carbamazepine and Lamotrigine Plasma Concentrations in Epileptic Patients during Optimising Therapy

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SUMMARY

Therapeutic monitoring of antiepileptic drugs is important in process of optimisation of therapy of epileptic patients. Carbamazepine (CBZ) and Lamotrigine (LMT) are important drugs in therapy of epileptic patients which requires the monitoring of concentration of these drugs in serum. Our study aim was the comparison and interpretation of the results of routine therapeutic monitoring of Carbamazepine and Lamotrigine in spotlight of antiepileptic therapy optimisation. We have analyzed 74 blood samples of epileptic patients who were in therapy with Carbamazepine or Lamotrigine. High pressure liquid chromatography was used in determining the serum concentration of above mentioned drugs. Results of our study show the positive correlation between dosage and serum concentration of CBZ. (r = 0.78). The correlation coefficient between the dosage and serum concentration of LMT is higher than CBZ (r = 0.825). In the process of monitoring of serum concentration of CBZ, very important issue is the serum concentration of active metabolite named to carbamazepine-10,11-epoxide (CBZE). The correlation coefficient between the CBZ and its active metabolite was r = 0.57. During analysis of correlation between blood sampling time from last dose intake and serum concentration of respective drug in both drugs (CBZ and LMT) we have found the negative small correlation (r =–0.256 and r =–0.288). The results of our study contribute to other studies which confirm the complexity of therapeutic drug monitoring (TDM) process in general and particularly for CBZ and LMT. The process of TDM requires the selection of adequate analytical method and right appropriate interpretation of the serum concentration of these drugs.

Keywords: therapeutic drug monitoring, carbamazepine, lamotrigine

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1. INTRODUCTION

Different antiepileptic drugs (AEDs), varying in their spectrum of efficiency is prescribed for pharmacological treatment of different types of epilepsy (1).

Epilepsy affects about 5 persons in 1,000 and represents the most common serious neurologic disorder and many individual epileptic patients can require many years of, if not lifelong, treatment with antiepileptic drugs (2,3).

Currently, approximately 10 new antiepileptic drugs (AEDs) and numerous older agents are available to patients and physicians for the treatment of epilepsy (4).

In the last 2 decades, several new anticonvulsants have been introduced into routine clinical practice, trying to improve the anti-epileptic treatment. The advent of new AEDs is a welcoming development because these drugs produce an appreciable improvement in seizure control in many patients who had been refractory to older agents. Little good-quality evidence from clinical trials has occurred in support to the use of newer mono-therapy or adjunctive AEDs over older drugs or in support to the use of one newer AED in preference to another (5,6).

Concerning these facts, the old AEDs still remains the most prescribed AED over newer AEDs, despite the fact of a trend for some new AEDs to manifest better tolerance than older agents (7). Carbamazepine (CBZ), phenobarbital, phenytoin, and valproic acid are commonly prescribed antiepileptic drugs that are metabolized extensively and show complicated pharmacokinetic behavior that is influenced by other drugs. In the group of newer AED, the valuable used drugs are gabapentin, lamotrigine, topiramate, and oxcarbazepine, which have a narrow therapeutic index, and need the careful individualization of the dosage in order to optimize the clinical response (8-14).

Due to the nature of epilepsy, it is problematic to monitor AED treatment by direct observations of clinical response in the individual patient. Antiepileptic drugs are characterized with important inter-and/or intra-individual variation in pharmacokinetics, due to drug interactions and genetic polymorphism, with variability in dose concentration relationship, different susceptibility to adverse reaction and many of antiepileptic drugs correlate the clinical effect better with blood levels than with doses (15-17).

The pharmacological treatment of patients with epilepsy is one of the areas where therapeutic drug monitoring (TDM) has made the most significant contributions in optimization of therapy. The interpretation of plasma levels of AED in the light of the clinical situation of epileptic patients can markedly influence dose optimisation of this drugs (18).

Although the TDM for old AED is established, there are some discussions regarding r newer AEDs that routine serum concentration monitoring cannot be justified in the absence of studies designed to explore specifically their concentration response relationship, but a case for applying TDM of these drugs in individual patients can still be made (14,19,20).

Our study aim was to compare and interpret the results following the introduction of a routine therapeutic monitoring of Carbamazepine (CBZ) and Lamotrigine (LTG) service in spotlight of antiepileptic therapy optimisation and impact of blood sampling time in serum concentration of respective drugs.

2. MATERIAL AND METHODS

This retrospective study was carried out on 74 blood samples, collected from epileptic outpatients who were referred to the therapeutic drug monitoring in the department of Clinical Pharmacology of University Clinical (UCC) Center "Charite" in Berlin. From 74 samples, carbamazepine was measured in 44 of them, while lamotrigine in 30 samples.

Parameter	N	Mean	SE
Serum Conc. CBZ (mg/L)	44	15.45	9.57
Serum Conc. LMT (mg/L)	30	3.096	2.63

Table 1. The mean value and standard deviation of serum concentration of CBZ and LMT

Parameter	n	Mean	SE
Blood sampling from last CBZ dose (min)	44	705.456	256.75
Blood sampling from last LMT dose (min)	30	526.17	315.08

Table 2. The importance of blood sampling time from the last dosage time

Parameter	Serum Conc. CBZ (mg/L)
Blood sampling from last CBZ dose (min)	r =–0.256
Blood sampling from last LMT dose (min)	r =–0.288

Table 3. The correlation between blood sampling time and serum concentration of CBZ and LMT

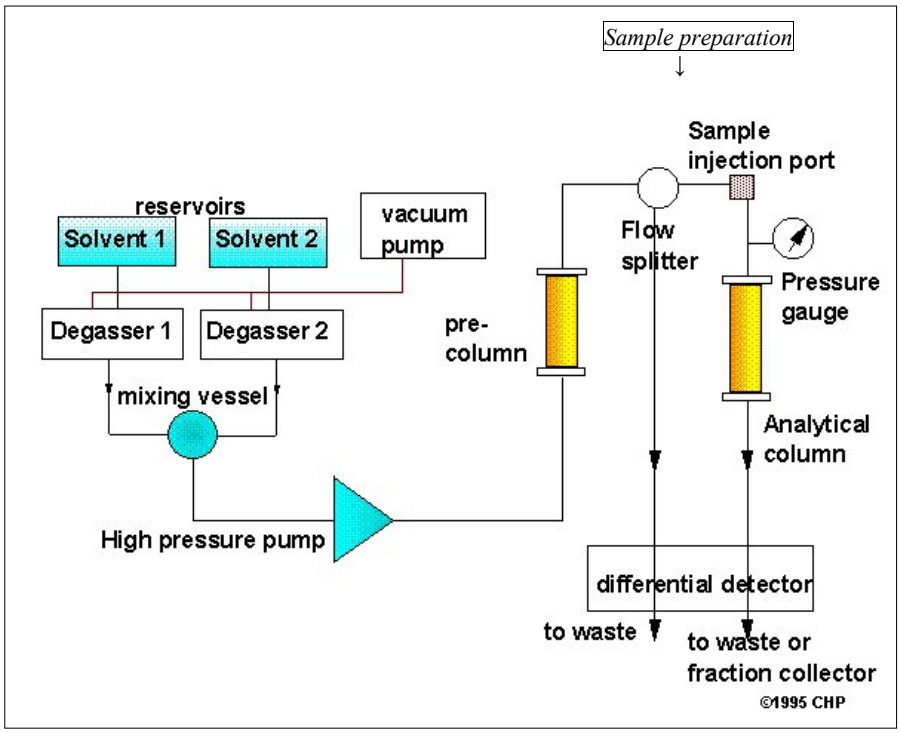
The blood samples have been collected from epileptic inpatient and outpatients treated in the Departments of Neurology of UCC "Charite". The serum concentration of above drugs has been determined in the steady state concentration. The serum concentration of these drugs has been measured by high pressure liquid chromatography (HPLC). For TDM of CBZ we have used the isocratic system of Shimadzu HPLC (*HPLC pump–Shimadzu model: LC-9A; Auto-injector–Shimadzu model: SIL-9A and UV detector–Shimadzu model: SDP-6AV*).

For determination of CBZ and Lamotrigine by HPLC System Shimadzu, we have used the commercially reagents and procedure supplied by Chromsystems Instruments and Chemicals GmbH (Chromsystems-Munich, Germany). For sample preparation of CBZ, we have used the methods established by above mentioned company. For sample preparation, we have used patient serum and Internal Standard, Precipitation Reagent Stabilisation Buffer and calibration solution from commercial company.

Serum samples were stored at –70°C. Using the chromatographic methodology, we have obtained the level of carbamazepine-10,11-epoxide (CBZ-E), as active metabolite of CBZ.

The stability of method has been checked by calibration stability, which is controlled by daily running of controls to check the intra and inter assay specificity. Between run, coefficients of variation were less than 8% for all assays in all laboratory analytical systems and were in the accepted analytical range.

Statistical analysis of the data was made using the SPSS for windows (version 12.0) and Microsoft Excel. Parametric tests were used when the data had a Gaussian distribution (Student-t test and Pearson correlation coefficient, mean and SD).



Scheme 1. Schematic of an HPLC procedure for determination of CBZ and LMT serum concentration

3. RESULTS

The results of our study are obtained from analyses of samples during routine service of therapeutic drug monitoring performed in UCC "Charite" Berlin.

We have analyzed the serum concentration of CBZ and LMT measured by method of high pressure liquid chromatography (HPLC). The serum concentration of CBZ and LMT have been analyzed in terms of correlation

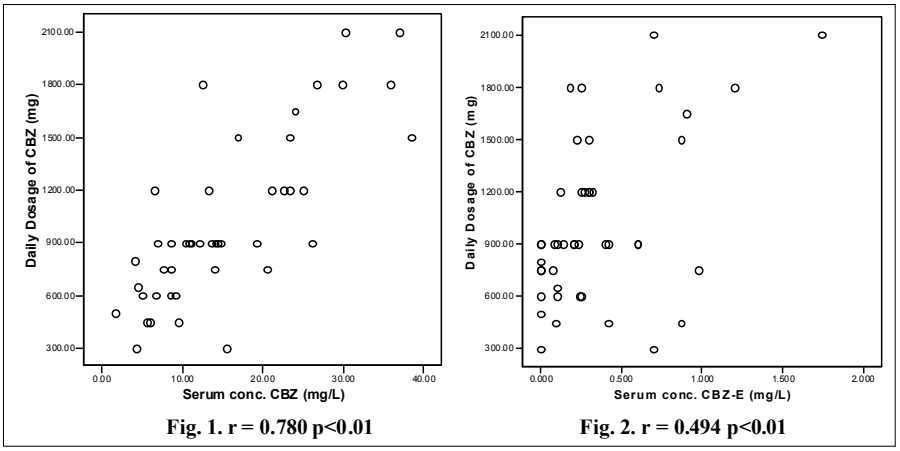


Fig. 1. r = 0.780 p<0.01

Fig. 2. r = 0.494 p<0.01

FIGURE 1&2. Correlation between daily dose of CBZ and serum concentration of CBZ serum (Fig.) and between daily dosage of CBZ and serum concentration of active metabolite of CBZ (Fig. 2)

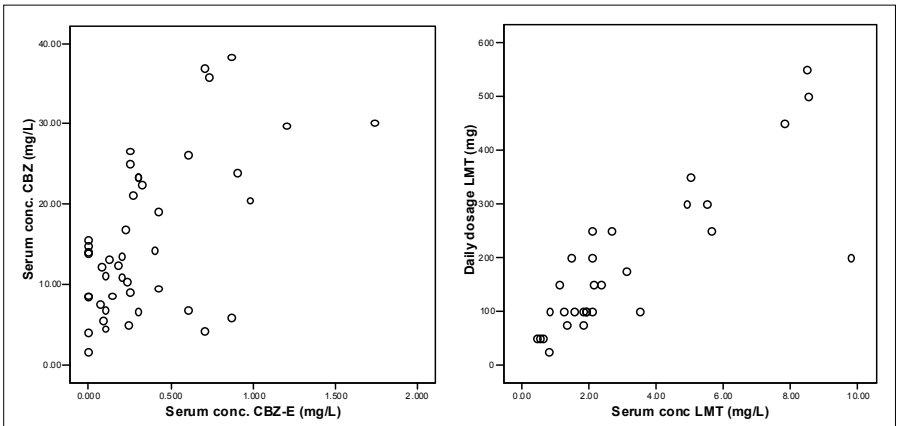


Fig. 3. r = 0.570 p<0.01

Fig. 4. r = 0.825 p<0.01

FIGURE 3&4. Correlation coefficient between the CBZ as primary drug and CBZ-E as active metabolite of CBZ (Fig 3.) and high value correlation between the daily dosage and serum concentration of LMT (Fig. 4)

between daily dosage and serum concentration of these drugs, correlation of CBZ and active metabolite of CBZ named CBZ-E and we have analyzed the correlation coefficient between time of serum concentration of drug and time of blood sampling from last dosage intake of respective drug.

In table 1 we have presented the mean value and standard deviation of serum concentration of CBZ and LMT. The mean value of CBZ is higher than max. value of target range for serum concentration for CBZ (4-12 mg/L) while the mean value of serum concentration of LMT is in normal range (1-4 mg/L).

In the figure 1 we have presented the correlation between daily dose of CBZ and serum concentration of CBZ serum (r=0.78 p<0.01) while in figure 2 we have presented the same correlation relation between daily dosage of CBZ and serum concentration of active metabolite of CBZ (r.0.494 p<0.01). The obtained results shows much high correlation between daily dose and serum concentration of CBZ compared with correlation between relation between daily dosage of CBZ and serum concentration of active metabolite of CBZ (carbamazepine-10,11-epoxide)

Due to therapeutic importance of CBZ-E, in figure 3 we have presented the correlation coefficient between the CBZ as primary drug and CBZ-E as active metabolite of CBZ. The results show the moderate correlation between these 2 components.

In the figure 4 we have showed the high value correlation between the daily dosage and serum concentration of LMT.

The importance of blood sampling time from the last dosage time we have presented in the table 2. The data from this tab. shows the high variability of blood sampling time for CBZ especially for LMT.

In the table 3 we have presented the correlation between blood sampling time and serum concentration of CBZ and LMT. In both cases, we have obtained the small negative correlation.

4. DISCUSSION

In the light of presented literature, establishing the antiepileptic serum level is a widely accepted modality which facilitates control of drug dosage regimen, evaluation of therapeutic effect and reveal of drug patient compliance. The interpretation of TDM results depends on several complex factors as follows: the pharmacokinetics of measured drug, co-medication, the selected analytical method and adequate sampling time. Several studies have documented that the monitoring of antiepileptic is frequently done inappropriately (21-23).

In the TDM of CBZ, the important step is determination of serum concentration of CBZ and its active metabolite called CBZ-E. The correlation coefficient between daily dosage and serum concentration of CBZ in adults, presented by Kumps is r=0.385 (24).

Almost same correlation coefficient has presented the Strandjord et all (r = 0.35, p < 0.01) and Desoky et all, *r*=0.5; *P*-0.001 (25,26).

The result of our study shows much higher correlation comparing with above mentioned studies. (r = 0.78 p<0.01).

The correlation coefficient between the daily dosage of CBZ and its active metabolite (CBZ-E) is less than the correlation between daily dosage and serum concentration of CBZ. (r=0.494 p<0.01 vs. r = 0.78 p<0.01).

Conversion of CBZ to carbamazepine-10,11-epoxide (CBZE) through cytochrome P450 (CYP) 3A4 as main metabolic pathway uses a mass of about 30 and 50% of the dose administered to patients during antiepileptic treatment with CBZ (27,28).

These facts are attributing the important role of this active metabolite in the therapeutic value of CBZ (29,30).

The TDM of CBZ, using the chromatography system, enables to obtain the results of CBZ-E, while the determination of CBZ-Z by immunoassays methods is not possible.

In our study we have obtained the moderate correlation between CBZ and CBZ-E level, r=0.570 p<0.01 and it is almost in same range with other authors. (Mihaly et all, y = 0.1 lx + 0.58; n = 34, *r* = 0.495; *P* <0.05; Fahiolino et all, n =

69, r = 0.476, ($p < 0.001$) (31).

The results of our study and the results of other authors shows for heterogeneous value of correlation coefficient between the daily dosage and serum concentration of CBZ and this relation is more complicated because the clinical effect of CBZ depends from its active metabolite too. These facts confirm the importance of TDM in the dose optimisation.

The correlation between daily dose and serum concentration of LMT in our study is high correlation (r=0.825 $p < 0.001$). Nevertheless, this correlation is smaller than the correlation coefficient between daily dose of LMT as mono-therapy and serum concentration found by Devulder et all (r = 0.9475 per p = 0.0041) and similar with results of author Morris et all $r^2=0.83$ $p<0.01$) which has presented the correlation between the dose and serum concentration of LMT in patients who have received co-medication with other antiepileptic drugs (32,33).

The important fact in the TDM is the definition of therapy as mono-therapy or poly-therapy due to evident impact of other drugs in serum concentration of measured drugs.

The limitation of our study were the inability to define has the patient received the CBZ or LMT as mono-therapy or with other antiepileptic drugs.

Important factor to obtain the valid serum concentration of monitored drugs is the sampling time. Recommended sampling time for CBZ and LMT is pre-dose (34).

The negative small correlation coefficient between the serum concentration and blood sampling time from last dose of CBZ or LMT do not represent appropriate information for importance of this procedure in the process of TDM. For definition of importance of blood sampling time, we propose the randomised controlled prospective study.

5. CONCLUSIONS

Results of our study show the **positive correlation** between dosage and serum concentration of CBZ. (r = 0.78; $p<0.01$). The correlation coefficient between the dosage and serum concentration of LMT is higher than CBZ (r = 0.825; $p<0.01$). In the process of monitoring of serum concentration of CBZ, serum concentration of active metabolite named to carbamazepine-10,11-epoxide (CBZE) is a very important issue. The correlation coefficient between the CBZ and its active metabolite was r = 0.57.

Our results for both drugs shows **negative low correlation** between the time from last dose intake and time of blood sampling of CBZ or LMT (r = -0.256 respective r =–0.288 for $p<0.01$). The correlation coefficient between the daily dosage of CBZ and its active metabolite (CBZ-E) is less than the correlation between daily dosage and serum concentration of CBZ. (r=0.494 $p<0.01$ vs. r = 0.78 $p<0.01$).

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