

## Lamotrigine therapeutic drug monitoring in a tertiary epilepsy centre

### Monitorização Terapêutica da Lamotrigina em um Centro Terciário de Epilepsia

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#### ABSTRACT

**Objective:** to review the experience with lamotrigine therapeutic drug monitoring in a tertiary epilepsy centre aiming to characterize the plasma concentrations profile. **Methods:** inclusion of adults and children to whom lamotrigine concentrations were requested from October 2008 to April 2010. A chromatographic method was validated to determine lamotrigine concentrations. Reference range adopted (plasma): 2.5-15.0 mg/L. **Results:** 115 patients were included (86 adults, 29 children). Mean±standard deviation lamotrigine dosages for adults and children were statistically different (5.1±2.0 versus 7.4±3.4 mg/kg/day respectively,  $p<0.0001$ ), so as lamotrigine concentrations (5.13±4.0 versus 9.0±5.6 mg/L respectively,  $p=0.0006$ ). Approximately 68% of all quantifications were within the reference range. From the 29 quantifications below 2.5 mg/L, 27 corresponded to lamotrigine+enzyme inducers therapies. There was no correlation between lamotrigine concentrations and dosages neither for pediatric nor for adult groups. Patients on monotherapy had lamotrigine concentrations significantly higher than those on lamotrigine+inducers therapies ( $p<0.001$ ), and patients on lamotrigine+valproic acid therapy had lamotrigine concentrations higher than those on lamotrigine+inducers ( $p<0.001$ ). There was no significant difference among mean dosages according to different comedications. **Conclusion:** our observations about the influence of polytherapies on lamotrigine pharmacokinetics confirm the relevance of quantifying this antiepileptic drug plasma concentrations in the process of treatment optimization.

**Keywords:** epilepsy, lamotrigine, therapeutic drug monitoring

#### RESUMO

**Objetivo:** revisar a experiência de um centro terciário de epilepsia com a monitorização terapêutica da lamotrigina objetivando caracterizar o perfil de concentrações plasmáticas encontradas. **Métodos:** inclusão de todos adultos e crianças para os quais solicitou-se quantificação plasmáticas de lamotrigina de Outubro/2008 a Abril/2010. Um método cromatográfico foi validado para determinar as concentrações de lamotrigina. Intervalo de referência adotado (plasma): 2.5-15.0 mg/L. **Resultados:** 115 pacientes foram incluídos (86 adultos, 29 crianças). Média±desvio-padrão das doses de lamotrigina para adultos e crianças foram significativamente diferentes (5.1±2.0 versus 7.4±3.4 mg/kg/dia respectivamente,  $p<0.0001$ ), assim como as concentrações (5.13±4.0 versus 9.0±5.6 mg/L,  $p=0.0006$ ). Aproximadamente 68% das quantificações estavam dentro do intervalo de referência. Das 29 quantificações abaixo de 2.5 mg/L, 27 correspondiam a associações lamotrigina+indutores enzimáticos. Não houve correlação entre concentrações e doses de lamotrigina. Pacientes em monoterapia tiveram concentrações de lamotrigina significativamente maiores do que pacientes utilizando lamotrigina+indutores enzimáticos ( $p<0.001$ ); pacientes em uso de lamotrigina+ácido valproico apresentaram concentrações maiores comparativamente àqueles em uso de lamotrigina+indutores ( $p<0.001$ ). Não houve diferença significativa entre doses médias de acordo com diferentes comedicações. **Conclusão:** a influência de politerapias sobre a farmacocinética da lamotrigina confirma a relevância de se quantificar as concentrações plasmáticas deste antiepilético no processo de otimização terapêutica.

**Palavras-Chave:** epilepsia, lamotrigina, monitorização terapêutica

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## INTRODUCTION

Lamotrigine (LTG) is an antiepileptic drug (AED) approved to be prescribed in monotherapy or polytherapy to control partial epileptic seizures, primarily and secondarily generalized tonic-clonic seizures, absence seizures and the drop-attacks associated to Lennox-Gastaut syndrome<sup>1</sup>.

Although therapeutic drug monitoring (TDM) is considered an important tool to optimize the treatment through the possibility of individualizing dose regimens, its applicability to LTG is still controversial<sup>2,6</sup>. The relation between LTG plasma concentration values in steady state and the dosages used in clinical practice, although linear, can widely vary interindividually<sup>7,9</sup>. Therefore, the LTG plasma levels related to clinical efficacy may overlap those related to signs of toxicity in the same group of patients<sup>2,3,7,10-14</sup>.

Age, comorbidities associated with epilepsy, pregnancy and drug interactions are the major sources of the interindividual pharmacokinetic variability attributed to LTG<sup>7,13,15,16</sup>. For instance, when co-prescribed with AED such as the enzyme inducers carbamazepine (CBZ), phenytoin (PHT) and phenobarbital (PB), the metabolism of LTG is significantly increased (elimination half-life is shortened); oppositely, LTG elimination half-life is considerably longer when it is co-prescribed with valproic acid (VPA), an enzyme inhibitor AED. Besides its contribution to the therapy individualization process, TDM is also a valuable tool when investigating cases of poor compliance and suspected intoxications<sup>3,17</sup>.

The present study revised the experience with LTG TDM data in a tertiary epilepsy centre aiming to characterize the plasma concentrations values profile found in this context.

## PATIENTS AND METHODS

### Patients

All adult and pediatric patients with epilepsy in the Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto (HCFMRP) to whom LTG plasma level quantifications were requested from October 2008 to April 2010 were included in this study. A database was generated in Microsoft Excel to allocate the LTG plasma concentration values, so as the patients' clinical and demographic characteristics. All data were obtained from patients' medical records. The classifications of types of seizures and types of epilepsy were performed according to the proposed by the International League Against Epilepsy<sup>18,19</sup>. When more than one LTG plasma level was obtained in different moments for the same patient, the most recent value was considered for analyses. Patients taking LTG for other conditions than epilepsy were not included in this study. This research was approved by the HCFMRP Ethics Committee.

### Analytical procedures

The high-performance liquid chromatography with ultraviolet

detection (HPLC-UV) method validated to determine the LTG plasma concentrations was adapted from Angelis-Stoforidis and colleagues (1999)<sup>20</sup>. Briefly, the method was consisted of a 4 mL venous blood sample collected in heparinized tube previously to the morning LTG dose ingestion (trough level). The sample was centrifuged and the plasma stored at -20°C until analysis (not more than one week after sampling). The protein precipitation was performed with acetonitrile, and the internal standard used was the 5-ethyl-5-p-tolylbarbituric acid. The supernatant was dried under room temperature air flow, and the residue reconstituted in 100 µL hexane + 200 µL mobile phase (75% acetate buffer 0.25 M pH 4.4 : 25% acetonitrile). The lower layer (100 µL) was analyzed using a LiChroCART® 1254 Merck column (LiChrospher® 100, RP8, 5µm), coupled with a LiChroCART® 44 Merck pre-column (LiChrospher® 100, RP8, 5µm). Quantitation was performed by measurement of UV absorbance at 220 nm. The analytes separation in clinical samples was reached in less than 25 min. Every reagents and solvents used were HPLC grade. The reference range adopted by the centre for LTG TDM was 2.5 to 15.0 mg/L of plasma<sup>21</sup>.

### Statistical analysis

Descriptive statistics was used to show demographic and clinical data obtained from patients' medical records. Unpaired two-tailed t-test, Mann-Whitney nonparametric two-tailed test, Fisher's exact test, correlation coefficients (r<sup>2</sup>) and Kruskal-Wallis nonparametric test with Dunn's multiple comparisons post test were used as pertinent, and the level of significance adopted was p<0.05. Statistics were performed using GraphPad Instat 3.01 for Windows.

## RESULTS

A total of 115 patients were included in the present study. Their demographic and clinical characteristics are listed in Table 1. The mean±standard deviation (SD) age of the group (n=115) was 32.9±17.4 years. Gender distribution both for adults and children is displayed as the ratio "total number of male subjects/total number of female subjects".

High rates of refractory epilepsy were observed (78% from all adult patients and approximately 62% of the pediatric patients). Regarding the epilepsy type most frequently found in our sample (localization-related epilepsy, diagnosed in approximately 90% of the adults and 55% of the children), 59 patients out of 77 and 14 patients out of 16, respectively, had symptomatic etiology.

For pediatric patients, the mean±SD LTG dosage prescribed was 7.4±3.4 mg/kg/day. Adults had a mean±SD LTG dosage of 5.1±2.0 mg/kg/day. Mean dosages for adults and children were statistically different (p<0.0001; unpaired two-tailed t-test). Noteworthy, only 3% of adults and of children were in use of LTG not associated to any other AED.

Adverse events were spontaneously reported by 15.6% of the patients; somnolence was the most prevalent complaint (7/115).

Table 1. Patients demographic and clinical characteristics (n=115)

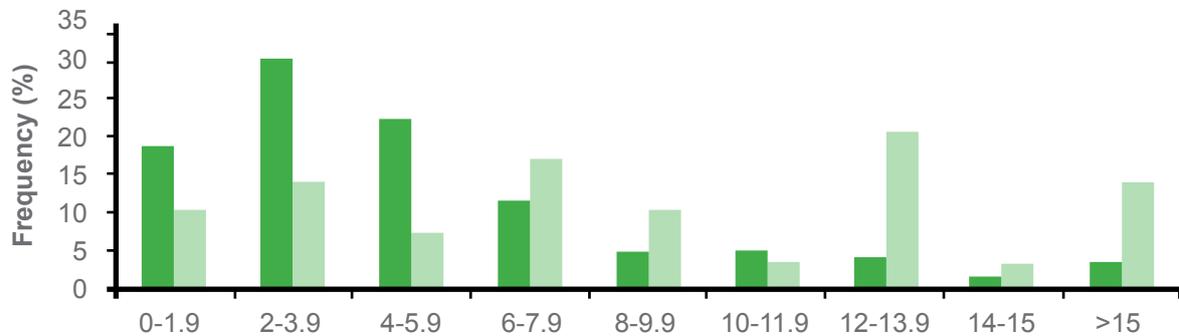
	Adults (n=86)	Children (n=29)
Age in years <sup>a</sup>	40.2±13.6 (18-76)	11±3.5 (4-17)
Male/Female	41/45	18/11
Refractory epilepsy	67 (78%)	18 (62%)
Type of epilepsy <sup>b</sup>		
Localization-related epilepsy	77 (90%)	16 (55%)
Generalized epilepsy	6 (7%)	10 (35%)
Undetermined	3 (3%)	3 (10%)
LTG dosage in mg/kg/day <sup>c</sup>	5.1±2.0	7.4±3.4
LTG monotherapy	2 (2%)	1 (3%)
LTG + other AED	42 (49%)	19 (66%)
LTG + other drugs	1 (1%)	0
LTG + other AED + other drugs	41 (48%)	9 (31%)
Adverse events reports	15 (17%)	3 (16%)

a: mean±standard deviation (range);  
b: International League Against Epilepsy classification;  
c: mean±standard deviation;  
AED: antiepileptic drugs; LTG: lamotrigine.

Figure 1 illustrates, in terms of frequencies, the drug association profiles mentioned in Table 1. Because of the wide variety, psychotropics, gastric ulcer and antihypertensive treatments, among others, are categorized as “other drugs”. Benzodiazepines (BZD) include clobazam (CLB), clonazepam (CNZ), nitrazepam (NZP), diazepam (DZP) and flurazepam (FZP). Carbamazepine is

the AED most frequently prescribed to adults (present in 53.5% of the prescriptions), followed by the benzodiazepine CLB, used by 52.3% of the adults. Among children, VPA was the most frequently prescribed AED (used by 51.7% of the patients included), followed by the benzodiazepine CLB (prescribed to 37.9% of the pediatric population).

**Figure 1.** Associated drugs prescribed to the patients (n=115). Black bars are adults’ data, while white bars are referred to children’s data. BZD: benzodiazepines; CBZ: carbamazepine; DPH: phenytoin; ESM: ethosuximide; GBP: gabapentin; LEV: levetiracetam; OXC: oxcarbazepine; PB: phenobarbital; TPM: topiramate; VGB: vigabatrin; VPA: valproic acid.



Means±SD LTG plasma concentrations differ significantly between children and adults ( $9.0\pm 5.6$  versus  $5.13\pm 4.0$  mg/L, respectively,  $p=0.0006$ ), according to the Mann-Whitney nonparametric test. Figure 2A shows the distribution of LTG plasma concentration values for the 115 patients in terms of frequency (% of patients) as a continuum. Regardless of age, 80% of the subjects had LTG plasma concentrations below 10 mg/L. Figure 2B also displays the LTG plasma concentration values in terms of frequency but arranged in relation to the reference interval adopted by the centre (2.5–15.0 mg/L). Approximately 68% of

all concentrations measured were within the reference interval (66.3% of the adults and 75.8% of the children). There was a slight significant difference between the frequency of adult patients who had concentrations below the lower limit of the interval compared to children ( $p=0.04$ ; Fisher’s exact test). Although 41.4% of the pediatric population had LTG concentrations above 10 mg/L in comparison to the 11.6% of the adult population, the difference between both age groups regarding the frequency of patients with LTG plasma concentrations above the upper limit of the interval is considered not quite different ( $p=0.06$ ).

**Figure 2.** Lamotrigine plasma concentrations values distribution for adult patients (black bars) and children (white bars) in terms of frequency (%) as a continuum (A) and in relation to the reference interval adopted by the centre (2.5 – 15.0 mg of lamotrigine/mL of plasma; B).

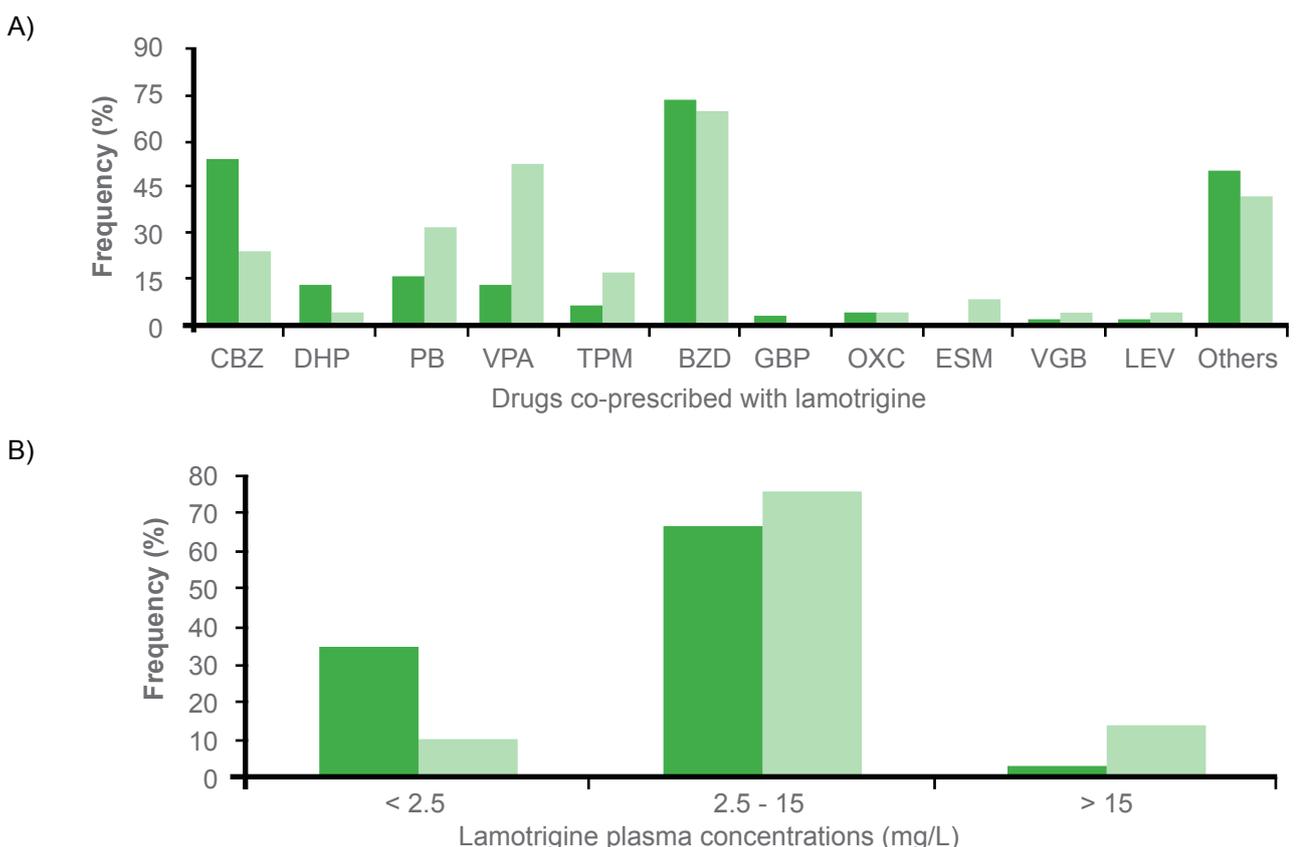
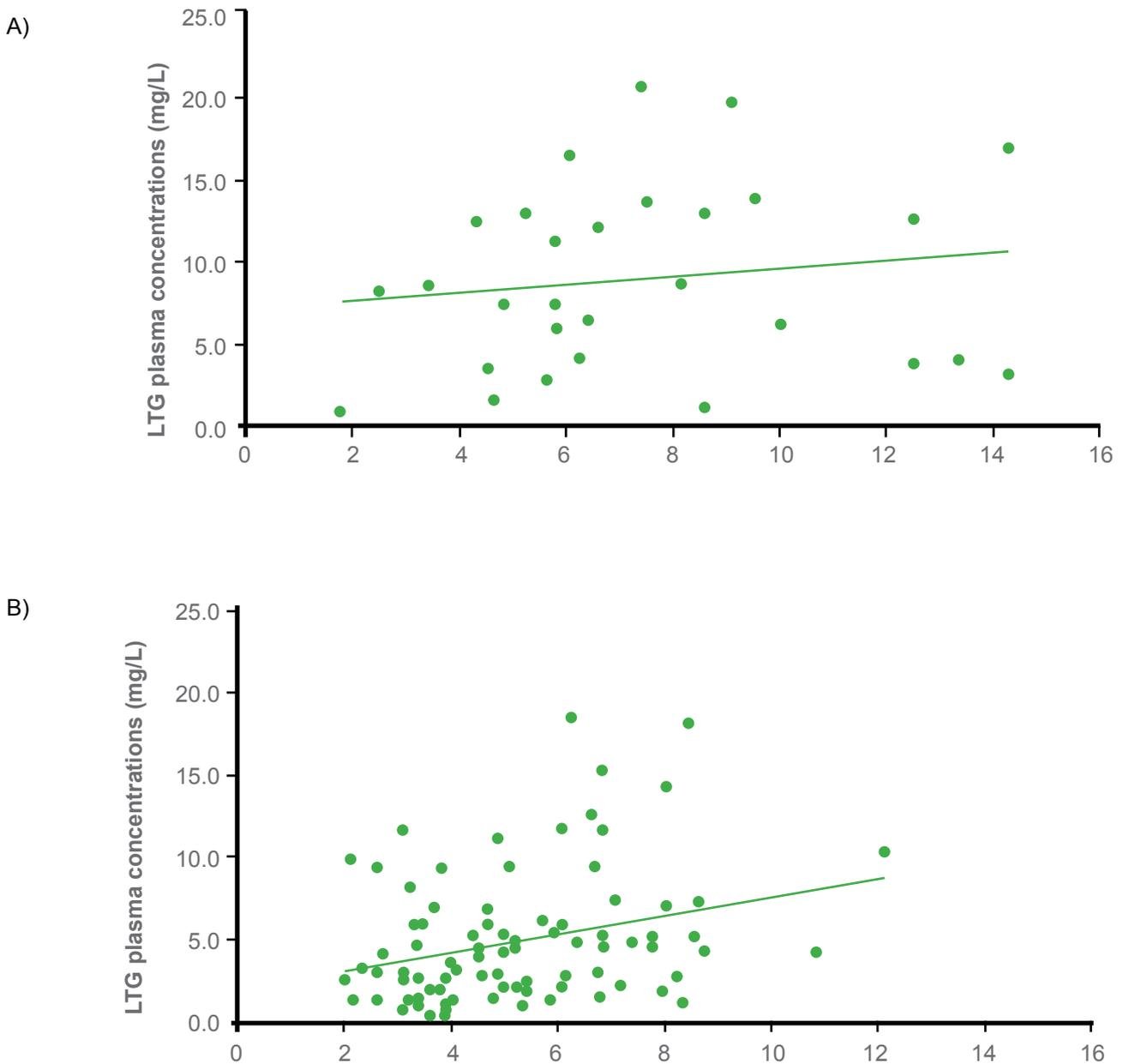
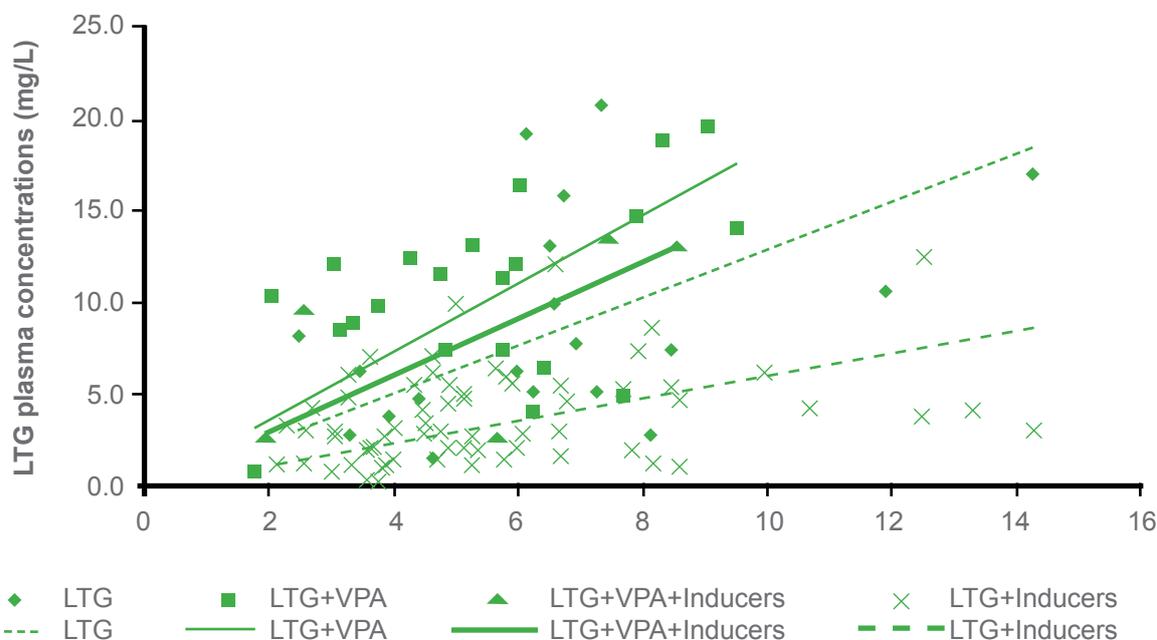


Figure 3 illustrates the lack of correlation between LTG plasma concentration values (mg/L) and LTG dosages (mg/kg/day) both for pediatric ( $r^2=0.02$ ; 3A) and adult groups ( $r^2=0.08$ ; 3B). When LTG plasma concentrations quantified for different dosages are displayed in relation to the comedication and regardless of age (Figure 3C), it is evident the higher LTG levels resulted from the co-prescription

with VPA, so as the lower levels caused by combinations of LTG and enzyme inducers AED. As highlighted by Bootsma and colleagues (2008)9, LTG clearance is inversely related to the slope of the trend line; hence, Figure 3C clearly shows how LTG+VPA therapies increase LTG concentrations (decrease in LTG clearance), while LTG+enzyme inducers decrease LTG concentrations (increase in LTG clearance).

**Figure 3:** Correlations between LTG plasma concentrations (mg/L) and LTG dosages (mg/kg/day) for children (3A) and adults (3B). 3C: effect of different AED associations on LTG plasma concentrations versus dosages (n=115). LTG: lamotrigine; VPA: valproic acid.





Mean LTG plasma levels $\pm$ SD (mg/L) and mean dosages $\pm$ SD (mg/kg/day) were calculated for each of the four groups (classified according to comedication only). Patients on LTG monotherapy (n=19) had a mean LTG concentration of  $8.9\pm 5.7$  and mean dosage of  $6.6\pm 2.9$ ; patients on LTG+VPA (n=21) had a mean concentration of  $10.7\pm 4.7$  and mean dosage of  $5.5\pm 2.2$ ; patients on LTG+VPA+inducers (n=5) had a mean concentration of  $8.4\pm 5.3$  and mean dosage of  $5.2\pm 2.9$ , and patients on LTG+inducers (n=70) had a mean concentration of  $3.8\pm 2.5$  and mean dosage of  $5.5\pm 2.6$ . In accordance to the Kruskal-Wallis nonparametric test with Dunn's multiple comparisons post test, patients on LTG monotherapy have LTG plasma concentration values significantly different from those on LTG+inducers therapies ( $p<0.001$ ), and patients on LTG+VPA therapy have LTG plasma concentrations values significantly different from those on LTG+inducers therapies ( $p<0.001$ ). There was no significant difference among mean dosages according to different comedication groups ( $p=0.39$ ).

From the seven LTG plasma concentrations above 15.0 mg/L, three were from patients taking LTG+VPA and the other four were from patients on LTG monotherapy (in these four cases, LTG was combined with non-inducers/non-inhibitors drugs). Three out of these seven patients with LTG concentrations  $>15$  mg/L spontaneously reported somnolence as an adverse event (two patients taking VPA), while the other four had no complaints. Noteworthy, from the 29 LTG plasma concentrations below 2.5 mg/L, 27 corresponded to LTG+inducers therapies.

## DISCUSSION

The main purpose of TDM in clinical practice is to provide data on the plasma concentration of a drug that may facilitate adjustments on therapeutic schemes ultimately aiming the best patient outcome. Clinical responses correlating better with drug concentration than with drug dosage is one of the assumptions behind the TDM rationale, and not being in full accordance with this rule was considered a sufficient factor to justify the irrelevance of monitoring the plasma concentrations of a given drug. In fact, the literature discouraging the use of TDM for LTG argues that there is no clear-cut correlation between plasma concentrations and clinical responses (nor

therapeutic neither toxic)<sup>7,22</sup>. It is important to acknowledge, however, that patients with different levels of seizure control may behave differently in terms of AED concentrations tolerated and associated with therapeutic benefits. Comparisons among plasma concentration values, efficacy and tolerability data in heterogeneous groups (refractory epilepsy and seizure free or newly diagnosed patients) may drive to misleading conclusions about the reliability of TDM data and their applicability in clinical practice<sup>2,4,23</sup>.

Our sample displays an expressive percentage of patients with refractory epilepsy (Table 1). As stressed by Hirsch and colleagues (2004)<sup>24</sup>, these patients can tolerate and need high LTG plasma levels to achieve therapeutic benefits. Khinchi and colleagues (2008)<sup>6</sup> argue, however, that although patients treated in tertiary epilepsy centre could be able to tolerate high LTG plasma concentrations, it does not necessarily imply in a concentration profile always with elevated values. Figure 2 shows that approximately 80% of the patients included in this study had LTG plasma concentration values below 10 mg/L, and around 70% of the subjects had their concentration values within the reference range adopted by the centre (2.5-15.0 mg/L). It should be noted, however, the tendency to increased LTG plasma concentrations presented by the pediatric group in comparison to the adult group (Figure 2; mean $\pm$ SD  $9.0\pm 5.6$  versus  $5.13\pm 4.0$  mg/L, respectively). The LTG pharmacokinetic in children shows that the factor age, when taken isolated, is consistent with high LTG clearance values (low plasma concentrations), which may be from 35% to 125% higher than the clearance values found in adults<sup>25</sup>. This aspect probably justifies the medical position observed in our data of prescribing higher LTG dosages to children than to adults ( $7.4\pm 3.4$  versus  $5.1\pm 2.0$  mg/kg/day, respectively). Nevertheless, considering that LTG is mainly prescribed in polytherapy (an observation also present in our sample; Table 1), the marked influences of comedications on LTG pharmacokinetics should not be neglected<sup>3,26-28</sup>. The high frequency of VPA prescriptions to children (Figure 1) possibly contributes to the tendency to high LTG plasma concentration values observed in this group. Valproic acid is an important inhibitor of the

main LTG elimination pathway, the glucuronidation. This combination has the potential to cause a marked reduction on LTG clearance, eventually increasing its elimination half-life and its plasma concentration values. Co-prescriptions of LTG and VPA are common in the pediatric population, especially for those patients with refractory epilepsy<sup>29</sup>, and when this association is necessary, the clinical care should be doubled in order to avoid the risk of cutaneous rashes occurrence<sup>30</sup>.

The difference between the LTG plasma concentrations means for children and adults and the low concentrations values profile presented by the adult patients (Figure 2) could have been accentuated also by the high prevalence of CBZ prescriptions to these patients (Figure 1). Not only CBZ but also the other enzyme inducers (PB and PHT) can significantly accelerate the LTG metabolism, reducing its concentrations in plasma and its elimination half-life from 15-35 h (monotherapy) to 8-20 h<sup>15</sup>. Corroborating, from the 29 LTG plasma concentration values below 2.5 mg/L, 27 corresponded to associations between LTG and enzyme inducers.

These different effects of comedications over the pharmacokinetics of LTG are evident on Figure 3C, where it is possible to observe, through the slope of the trend lines, how associations between LTG and enzyme inducers correspond to higher clearance and decreased plasma concentrations, while the combination LTG+VPA is associated with reduced clearance and higher LTG plasma concentrations. In accordance with the Figure 3C and with the previously published by Hirsch and colleagues (2004)<sup>24</sup> and Bootsma and colleagues (2008)<sup>9</sup>, the analysis of the LTG plasma concentrations related to the comedications shows means values significantly higher in patients using LTG+VPA in comparison to patients using LTG+enzyme inducers. Noteworthy, however, is that the dosages prescribed to patients classified according to the comedications do not show any statistically significant difference, what would be expected in clinical practice<sup>9</sup>. More important than considering age as a guiding factor to define posology is considering the existence of other AED being co-prescribed with LTG. This approach is advocated not only in the manufacturer's recommendations, but also in the clinical protocol to be followed by the Brazilian public health care system in cases of patients with epilepsy<sup>31</sup>, which proposes the following maximum LTG dosages regardless age: 1-5 mg/kg/day for monotherapy, 5.1 mg/kg/day for combinations with VPA and 5-15 mg/kg/day for combinations with enzyme inducers.

Deeper observations on possible correlations between efficacy/tolerability of LTG and its plasma levels are limited in this study due especially to the fact that this work has adopted a cross-sectional rather than a longitudinal analysis, i.e., there was no follow-up of the patients included in order to establish an individual therapeutic range that could be correlated with a satisfactory or unsatisfactory seizure control. Regarding tolerability, bearing in mind that this observation relies on spontaneous complaints of adverse effects, our data shows that from the seven analyzes with LTG concentrations above 15.0 mg/L only three corresponded to manifestations of adverse events (from a total of 18 spontaneous complaints), what reaffirms the previously mentioned about the tolerability of the patients with refractory epilepsy to high LTG concentrations. Reports of adverse effects by patients with low LTG plasma concentrations may result, at least in part, from pharmacodynamic interactions. Despite the LTG plasma concentration value, tolerability may be reduced in patients using CBZ concomitantly<sup>22</sup>.

Different reasons can justify the applicability of TDM for LTG. Cases of poor compliance, polytherapies, pregnancy and suspected intoxications are often highlighted in the

literature<sup>3,13,21,26,27</sup>. In summary, the present study aimed to present the LTG plasma concentrations profile in a tertiary epilepsy centre, and the most important aspect found in our sample that confirms the applicability of TDM for LTG in clinical practice is the high prevalence of polytherapies. Although we have confirmed a wide interindividual variation in the relationship between dosage versus plasma concentration in relation to age (Figure 3A, B), our observations about the influence of polytherapies on LTG pharmacokinetics (Figure 3C) show that quantifying this AED plasma concentrations especially in patients receiving other AED or about to have an AED started/stopped from the therapeutic scheme is pertinent in the process of individualizing the treatment.

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