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Original Article

RETROSPECTIVE STUDY ON THERAPEUTIC DRUG MONITORING OF LAMOTRIGINE IN INDIAN EPILEPTIC PATIENTS

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ABSTRACT

Objective: Antiepileptic drugs (AED) are administered either singly or in combination with other drugs. Their pharmacokinetics is influenced by drug-drug interaction & inter-individual variations. Lamotrigine (LTG) is a second order AED with similar constraints.

Hence studying the relationship between lamotrigine dosage and plasma concentration was undertaken to offer assistance in therapeutic regimen.

Methods: Pre-dose blood samples for lamotrigine estimation were obtained from 267 patients (138adults & 127children) including 2 pregnant women. Lamotrigine estimation was done by high performance liquid chromatography.

Results: In our study more children (73%) than adults (34%) were on adjunctive therapy with inhibitors (valproic acid) or inducers (phenytoin, carbamazepine, oxcarbamazepine). Irrespective of co-therapy lamotrigine level within therapeutic range with an optimal seizure control was obtained only in 76% of children and 65% adults. In case of polytherapy with valproic acid, when lamotrigine dose was maintained similar or lower than monotherapy, lamotrigine levels were 105% and 65% higher in adults and children respectively. Increased volume as observed in pregnancy had a remarkable influence on lamotrigine level. An increase in drug dose with an increase in gestation was required in both pregnant women to maintain the plasma level.

Conclusion: Inter-individual variations, co-medications and clinical conditions like pregnancy influence plasma lamotrigine level. Thus, drug monitoring is essential to obtain therapeutic efficacy for individual dose optimization.

Keywords: Lamotrigine, Adjunctive therapy, Inter-individual variation, Drug monitoring.

INTRODUCTION

Lamotrigine (LTG) is a broad spectrum second line anticonvulsant belonging to phenyltriazine class. It was approved by Food and Drug Administration (FDA) for both montherapy and adjunctive antiepileptic therapy for partial seizures in adults & pediatric patients older than 2 years [1, 2]. It is also approved for adjunctive use in Lennox-Gastaut syndrome and bipolar disorders. LTG has been experimented in virtually all types of epilepsy including absence and reflex seizures, status epilepticus and especially in epilepsy refractory to other medications [1, 3].

Approximately 55% of LTG in plasma is bound to proteins and has a volume distribution of 1.2 L/kg [4]. It exerts its antiepileptic effect by inhibiting the activation of voltage-sensitive sodium channels thereby stabilizing the neuronal membranes [5].

This further modulates the presynaptic release of an excitatory neurotransmitters (e.g.: glutamate, aspartate). It is also known to modulate the calcium and potassium currents [4]. LTG is rapidly absorbed from the gastro-intestinal tract and is only 50–60% bound to serum proteins [2]. It has a bioavailability of approximately 100% [6]. It is metabolized predominantly by glucuronidation pathway with UDP glucuronyl transferase to its inactive 2-N and 5-N glucoronide conjugates [3].

In healthy volunteers and patients receiving monotherapy, the mean half-life of LTG ranges from 23-37 hrs [7]. Its clearance is influenced by concomitant administration of other drugs. Enzyme inducing antiepileptic agents such as phenytoin or carbamazepine reduce its half-life to 8-20 hrs resulting in low drug level [8] while valproic acid (VPA) down-regulates the metabolism of lamotrigine, thereby extending its half-life to 60 hrs and necessitating a reduced dose [3]. Autoinduction is also a common phenomenon in LTG therapy. Autoinduction is usually complete within two weeks; with ~20% reduction in steady state serum/plasma concentrations if the dose is not changed [2]. The levels are influenced by other drugs like estrogens, progestin and HIV protease inhibitors [8]. In addition, its clearance is significantly reduced in case of hepatic and renal impairment. Also there is a fairly clear concentration threshold above which toxic side effects such as headache, nausea, dizziness, diplopia, ataxia, tremor, somnolence, blurred vision, increased seizure frequency and skin rash occur. In rare cases, complexes such as Steven Johnson Syndrome, toxic epidermal necrolysis etc also occur [9]. Besides inter-individual variation and drug-drug interactions, LTG levels also vary in pregnancy. Around 25% of epileptic patients are women in child bearing age [10].Though LTG is a safe drug in pregnancy with minimal fetal malformations, its clearance varies substantially with gestation[8,10]. All these factors lead to a large inter-individual variability in dose requirement further complicating the clinical use of LTG [2]. The role of therapeutic drug monitoring (TDM) for lamotrigine has been well emphasized in literature [6, 8, 11, 12].TDM for LTG is performed by analytical techniques like high-performance liquid chromatography (HPLC) [2, 8] and requires an expertise to process and report the test results. This limits availability of the testing facility to few referral centers. To the best of our knowledge, estimation of LTG is not available in India. The diagnostic centers were outsourcing the estimation to foreign laboratories. Hence we optimized this service in our laboratory using HPLC system. This clinical service has helped to achieve therapeutic goals for maximum efficacy. In the present article, we report a retrospective evaluation of LTG levels estimated in our laboratory over a period of two years.

MATERIALS AND METHODS

The study was approved by the Institutional Research Committee. A pre dose EDTA blood sample along with demographic details, drug dose, time from last dose, duration of therapy, co-medications and other relevant information including seizure frequency was obtained in the predefined clinical proforma. Pre-dose (trough)

blood samples were collected from all the subjects. The data was sorted as per the drug levels, dosage, concomitant therapy and clinical condition.

Lamotrigine Estimation

The plasma was separated immediately and was stored at -20^{0}C until analysis. A rapid and sensitive HPLC method was used. The estimation was done on Waters 1525 multisolvent delivery system pump and Waters 2487 variable wavelength UV–visible detector using a commercially available kit, ClinRep from RECIPE (Germany). After protein precipitation and dilution with internal standard, supernatant was injected using an auto sampler [13]. An internal standard recovery of 80-120 % was aimed to ensure quality of test results. Two level controls were processed in every batch for accuracy and calibrator was injected both at the start and end of the batch to assess precision and ensure minimal carry over during the analysis.

Data Analysis

The subjects were grouped based on age, gender and concomitant therapy. Based on concomitant therapy, the patient population was classified into three groups

Group I: Receiving Lamotrigine (LTG) monotherapy

Group II: Receiving LTG & inhibitor valproic acid (VPA)

Group III: Receiving LTG & inducers such as Phenytoin, carbamazepine or oxcarbamazepine

Statistical Analysis

All the study variables are given as mean ± standard deviation (SD).The statistical evaluation to assess the correlation of LTG dose, age, gender, co-medication etc. with LTG plasma level was performed using multivariate linear regression analysis. The regression analysis was performed using Epi Info software. (Epi Info™ 3.5.3)

Results

Patients Demographics

Over the period of 2years we had received 265 samples which included 127children and 138adults. In addition, there were requests for 2 pregnant women for whom drug levels were performed in all trimesters. Amongst the subjects, more adults were on monotherapy as compared to children and in case of polytherapy, valproic acid (VPA) was the preferred drug in both the groups. Unlike children the adult group comprised of more females as compared to the males (Table 1). No gender bias was noted in the drug level and hence the data is presented as a mean of both in each group (Table 1). Concentration/dose (C/D) ratio was also calculated to assess variation due to age and concomitant therapy. It is evident from Table 1 that adjunctive therapy with VPA increases C/D amongst children as well as adults.

Table 1: Lamotrigine Drug Level vs. Dose

	CHILDREN (n=127) Age(years) = 8±4			ADULT (n=138) Age(years) = 33±12		
	GROUP I	GROUP II	GROUP III	GROUP I	GROUP II	GROUP III
Total number of patients	34	85	8	91	34	13
Gender (male/female)	18/16	49/36	6/2	23/68	8/26	8/13
Lamotrigine dose (mg/kg/day)	4.5±2.6	5.0±2.9	6.9±1.0	5.5±2.0	3.9±1.9	4.3±1.7
Lamotrigine level (mg /l)	5.6±2.3	9.2±3.1	4.9±2.0	5.5±1.9	11.3±3.0	2.8±2.7
C/ D ratio (mg/l/mg/kg/day)	1.4±0.9	2.5±1.5	1.5±0.9	1.4±1.0	3.4±0.5	1.4±0.7

Lamotrigine dose/kg body weight when compared with the LTG concentrations (Figure 1) suggest that amongst children on similar LTG dose, the levels showed a 65% increase in case of co-medication with VPA while amongst adults, 105% increase in concentration was obtained even when LTG dose was reduced by 29%.

Table 2: LTG Levels in Our Study Population

	Children			Adult		
	Number Of Patients	Lamotrigine Dose (mg/kg/day)	Lamotrigine Level (mg/l)	Number Of Patients	Lamotrigine Dose (mg/kg/day)	Lamotrigine Level (mg/l)
Sub -Therapeutic	18(14%)	2.1±1.2	1.3±0.7	37(27%)	2.5±1.2	1.5±0.6
Therapeutic	96(76%)	5.0±3.8	7.4±3.03	90(65%)	4.4±2.6	7.30±3.41
Toxic	13(10%)	5.5±2.4	17.9±3.0	11(8%)	5.7±3.0	19.6±2.2

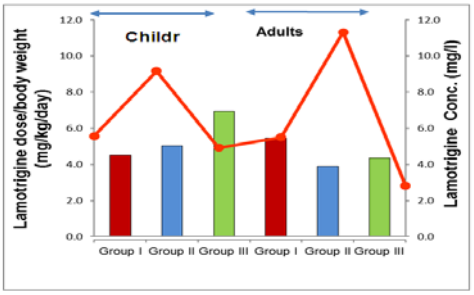
The inducers reduced the drug level notably amongst adults while in children a drug dose as high as 6.9mg/kg/day was required to attain therapeutic level i.e. 4.9mg/l as compared to children on monotherapy.

Therapeutic Range and LTG Levels

A therapeutic range of 3-14 mg/l was used in our laboratory based on a study done by Morris et al [8]. The reference range has been widely accepted and applied in management of patients with epilepsy [2-3, 8]. Approximately 76% of the children (n=96) and 65% of adults (n=90) had their LTG level within therapeutic range.

Irrespective of mono/polytherapy the LTG dose was between 100-400mg (209±160mg or 4.18±1.8 mg/kg/day).

LTG level in sub-therapeutic range with poor seizure control was noted in 14% children (n=18) and 27% adults (n=37).



Key: Bar Graph: Lamotrigine dose (mg/kg/day)**, Line Graph:** Lamotrigine level (mg /l)

Fig. 1: It shows correlation between lamotrigine concentration & dose

While LTG levels above therapeutic range were obtained in 10% children (n=13) and 8% adults (n=11) (Table 2).Increased drug levels were associated with toxic effects like rash, diplopia and dizziness in these patients.

On summarizing, around 70% of our patients showed a good seizure control and were within therapeutic range while 30% (n=79) had sub-therapeutic or toxic levels. An appropriate dose modification in lamotrigine as well as adjunctive drugs was warranted in these 30% patients to obtain seizure control.

Lamotrigine in Pregnancy

In both our patients an increase in LTG clearance during pregnancy was observed. In the first patient, the drug dose was increased from 75mg OD to 75mg BD and later to 100mg BD during the pregnancy. However, irrespective of the dose, her trough level ranged from 2–2.8mg/l while the peak level (2–3 hrs.after dose) ranged from 2.7–4mg/l throughout the pregnancy. The drug level in our second patient who was maintained on 100mg BD dropped from 4.9mg/l to 1.8mg/l in the first trimester. In the subsequent trimesters her dose was increased to 150mg BD and 200mg BD wherein her trough level was 3.8mg/l and 5.1mg/l respectively.

Source of Variation

Based on the values of partial regression coefficient and the p-value (Table 3) lamotrigine dosage was the most significant predictor of lamotrigine levels in adults, whereas it was moderately significant in children.

Table 3: Factors influencing lamotrigine concentration

	Children (R^2=0.34)		**Adult (R^2=0.83)**	
Factor	Partial Regression Coefficient (□)	p-value	Partial Regression Coefficient (□)	p-value
Lamotrigine dose	0.40	0.030 *	0.90	0.002 *
VPA dose	0.04	0.007	0.01	0.006
Age	0.29	0.038	0.02	0.127

*Statistically significant

The coefficient of determination (R^2) for children & adults was 0.34 & 0.83 respectively. Thus more than 80% of lamotrigine levels could be explained by factor such as lamotrigine dose in adults. While in children only 30% of LTG levels could be explained by LTG dose.

DISCUSSION

The HPLC based assay is favored to be adapted in routine practice. The therapeutic range of LTG plasma concentration reported in the literature range from 3-14 mg/l (2-3, 8). Studies have proven that LTG tolerability is highly correlated with LTG serum concentration [14].

Around 30 %(n=79) of patients in our study (Table 2) had sub therapeutic (1.5±0.6mg/l) or toxic levels (18.6±2.7mg/l) with poor seizure control. In these patients drug monitoring and subsequent dose modifications helped to optimize clinical care. Above results accentuate the point that monitoring of drug level is warranted in patients with infrequent seizures wherein drug levels will guide dose adjustments to obtain coveted plasma level. Desired drug level for each patient is the concentration at which seizures are well controlled without adverse effects. This varies between patients according to epilepsy syndrome, seizure types and disease severity [15].

In our study group, LTG was mainly used to control refractory seizures wherein several dose alterations and drug combinations are prescribed. In such patients inter-individual variations, drug-drug interaction etc. affect drug levels and monitoring would aid to achieve maximum clinical & therapeutic efficacy.

We have also observed that there is a large inter-individual variability in LTG metabolism which is further affected by the co-medications particularly inhibitors and inducers. VPA inhibits hepatic enzymes including LTG metabolizing enzyme UDP-glucorunyl transferase thereby decreasing LTG metabolism [16-17]. In our patients, children on same LTG dose showed a notably higher concentration when on co-medication with VPA (Figure 1). While the adults even though on a lower LTG dosage as compared to monotherapy had a higher LTG concentration due to VPA co-therapy. Thus, our findings suggest that a marked lamotrigine dosage reduction may be required if VPA is to be introduced to a patients therapy. Alternatively, addition of valproate can be used to increase low plasma LTG concentrations without increase in LTG dosage. We also observed that in case of polytherapy with VPA, when lamotrigine dose was maintained similar or lower than monotherapy, lamotrigine levels were 105% higher in adults and only 65% higher in children (Figure 1). This could be because of varied lamotrigine clearance. Lamotrigine clearance is higher in children [11, 18] and moderately reduced in adults [18].

The inducers (phenytoin, carbamazepine and oxcarbamazepine) also showed a remarkable reduction in levels in both the groups (children/adult). However a larger patient population would be required to obtain a profound correlation

Multivariate linear regression analysis showed that lamotrigine dose influence lamotrigine concentration (Table 3).The study by Morris et al [6] reported that there is a linear relationship between LTG dose and LTG concentrations particularly under the influence of type of co-medication. Similar results are also reported in Japanese [19] & white populations [20]. Influence of age on LTG serum concentration was reported by Bartoli et al [11] and also by Armijo et al [21]. Our data did not show any significant association between age & LTG level. No gender bias in LTG level has been reported in literature [17, 20] and the same has been observed in our study.

LTG is a safe drug in pregnancy with minimal fetal anomalies [22]. However, its metabolism is significantly altered due to an increase in plasma volume leading to a decrease in LTG level [8]. In both our patients an increase in LTG dose with gestation was required to maintain plasma levels. The variation could be attributed to an increase in glomerular filtration rate (GFR), plasma volume and/or total body water and increased estrogen levels [10]. All these factors cause an accelerated glucuronidation leading to decrease in the drug level. Thus, drug monitoring ensures a seizure free pregnancy with minimal fetal toxicity. The volume reduction in postpartum period would also result in an increase in LTG concentration [23] and hence a simultaneous reduction in LTG dose would be required to reduce toxicity. In addition to the drug-drug interaction, polymorphisms in the UDP-glucuronosyl transferase 1-4(UGT1A4) and UDP-glucuronosyl transferase-2B7 (UGT2B7) gene have been recently reported to influence LTG level [24].

CONCLUSION

In conclusion it is evident that LTG metabolism has a wide inter-individual variability and its clearance is influenced by co-medications and pregnancy. Genotype variations reported may also influence drug level and hence monitoring of lamotrigine plasma concentrations offers assistance in management of seizures.

CONFLICT INTERESTS

None

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