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Brief Communication

Lamotrigine serum levels: Ceiling effect in people with epilepsy in remission?

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ABSTRACT

Background: Antiepileptic drug titration in epilepsy remains mostly empirical. Since in practice seizure remission may be obtained with low doses, we aimed to determine whether patients in remission have lower lamotrigine levels than those with ongoing seizures.
Methods: Retrospective comparison of the distribution of lamotrigine levels among unselected patients in remission and with ongoing seizures. Remission was defined as 3 times the longuest interseizure interval and at least one year. Only trough levels were analyzed.
Results: Between 2009 and 2014, we identified 93 adults, among whom 10 were in remission. Patients in remission had significantly ($p = 0.008$) lower serum levels (median 2.3 mg/L, range: 0.7–8.2) than those with ongoing seizures (median 5.4 mg/L, range: 1.1–18.2). We did not find any patient in remission with levels higher than 8.2 mg/L. Distribution of dosages also differed among the groups, but less significantly (median: 175 vs 300 mg, $p = 0.03$).
Conclusion: An association between lamotrigine serum levels and seizure response can be observed. This suggests the existence of a ceiling level, above which remission is unlikely and should prompt antiepileptic medication switch rather than further up-titration of lamotrigine in drug-naïve patients with epilepsy.

1. Introduction

Prescription and titration of antiepileptic drugs (AEDs) remain largely empirical. It is common to increase the dosage, sometimes up to the appearance of adverse events, before concluding to resistance and either switching or adding AEDs. No clear ceiling dosages have indeed been determined for newer generation AEDs in terms of seizure control. It has been shown however that more than 90% of seizure-free patients were taking less than 300 mg of lamotrigine per day, suggesting that the chance to achieve seizure freedom at higher doses is small [1]. Defining a ceiling exposure would be particularly relevant in drug-naïve epilepsy patients, in whom the primary aim of the treatment is finding the right agent to achieve remission as quickly as possible. On the other hand, in people with refractory epilepsy, continued titration resulting in a relative reduction of the seizure frequency can still be valuable [2].

Interindividual variability of AEDs metabolism, due to genetic polymorphism, co-morbidities or co-medications, prevents establishing a direct correspondence between AED dosages and circulating exposure, assumed to correlate with clinical response, hence commanding dosage individualization [3]. This results in a stepwise increase in the search of the optimal dosage, potentially exposing patients to adverse events and to continued seizures even when maximal effective dosages are exceeded and AED switch would be preferable [2]. Therapeutic drug monitoring offers the opportunity to determine AED concentration exposure in patients, accounting for the genetic or acquired variability in AED metabolism [4,5].

Reference ranges of older-generation AEDs, such as phenytoin or carbamazepine, have been well determined and are widely accepted. Older generation AEDs are however decreasingly used [3,6]. New generation AEDs, such as lamotrigine, have been shown to be more effective (thanks to their better tolerability), thus explaining their progressive adoption as the standard of care in focal epilepsy [7], while their concentration monitoring is deemed less necessary.

Our aim was to explore the distribution of lamotrigine serum levels in a population of people with epilepsy, stratified between remission

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and ongoing seizures, in order to confirm that the former had lower serum levels and to identify a ceiling level associated with remission.

2. Methods

We reviewed retrospectively lamotrigine concentrations and the response to medication at the time of blood sampling. We collected all consecutive lamotrigine levels measured in patients followed at our centre between August 2009 and March 2014. We considered only the most recent measurement in patients having more than one analysis. Lamotrigine serum levels were measured at the Laboratory of Lavigny by high performance liquid chromatography [8]. We ascertained through chart review that all lamotrigine levels were measured in trough samples. Cases with an interval between last dosing and blood sampling of less than 6 h [3] and patients younger than 17 years were excluded (as some epileptic syndromes in children evolve towards natural remission).

Basic demographic data, pregnancy status and seizure history were collected from medical records, which in our institution are standardised with systematic reporting of the last seizure date. We defined remission according to the International League Against Epilepsy (ILAE) [9] as lasting three times the longest pre-treatment seizure-free interval (for example, a seizure every 3 months implies a seizure-free interval of at least 9 months) and more than one year. This rule of three has been recently validated on a statistical basis [10]. All seizure types were considered for the assessment of remission, including also auras. In case of insufficient documentation about the nature of a suspected seizure relapse, episodes were conservatively considered as seizures. Patients with breakthrough seizures due to an identified provocative factor (e.g. abusive alcohol intake or drug omission) were also considered as not in remission.

Patients receiving polytherapy were included. In these patients, we considered the remission to be associated with lamotrigine only if it was the last drug introduced; if a clear sequence could not be established, the case was excluded.

Data were described and analyzed by conventional non-parametric approaches. The relationship between concentrations and remission or ongoing seizures was then assessed using an analysis of variance (ANOVA) on log-transformed values. The model was further refined with the inclusion of polytherapy and daily dosage as covariates. The study was approved by the local ethic committee, consent was waived given the observational fully retroaspective nature of the study.

3. Results

We collected 168 patients with epilepsy, among whom 9 were excluded because of incomplete data and 46 because blood sample was drawn either less than 6 h after dosing or at an unknown time. We also excluded 20 pediatric patients. This left 93 patients for analysis.

All patient's details, lamotrigine dosage and level are shown in Table 1, none of them were pregnant at the time of sample. In seven patients, the syndromic classification was unclear. Comedication was valproate in 19 patients (40%), clonazepam/clobazam in 11 (23%), levetiracetam in 7 (15%), pregabaline in 7 (15%), carbamazepine in 4 (8%) and other in 9 (19%). Althogether, 7 patients were taking concomitantly a liver enzyme inducer (15%). Among patients on polytherapy, presence of liver inducer AEDs was not associated with higher LTG dosage (0.47, Mann–Whitney). Serum levels in patients in remission and those with ongoing seizures are shown in Fig. 1. Distributions of serum log levels differed also significantly ($p = 0.008$, Mann Whitney test) between patients in remission (median 2.3 mg/L, range: 0.7–8.2, geometric mean 2.4) and those with ongoing seizures (median 5.4 mg/L, range: 1.1–18.2, geometric mean 4.9). Among those in remission, 8 out of 10 had levels lower than 5 mg/l.

The ANOVA model confirmed that patients with ongoing seizures had roughly twice the average concentration of those in remission (relative increase by a factor 2.05, 95% confidence interval: 1.3–3.3, $p = 0.003$). The inclusion of the factors *polytherapy* and *daily dose* improved the model, showing both these covariates to be associated with higher concentrations (relative increase respectively 1.61, 95%CI: 1.20–2.13, and 1.44, 95%CI: 1.17–1.78), and thus probably mediated a part of the effect of the remission status (which decreased down to a factor 1.32, 95%CI: 0.83–2.08). ANOVA which was used to assess the role of the remission status on the daily dosage alone finds an association as well, with doses 1.6 times higher in patients with ongoing seizures (95%CI: 1.03–2.41), however with a smaller percentage of the variation explained by this model in comparison with the model using concentrations (R-squared: 5% versus 9%).

Within the group of patients with ongoing seizures, patients on monotherapy had significantly lower blood levels (median 3.8 mg/L, range 1.1–14.4) than those on polytherapy (median 6.0 mg/L, range 1.6–18.2, $p = 0.005$).

4. Discussion

4.1. Results

Our results reveal that patients with epilepsy in remission have significantly lower lamotrigine serum levels and daily dosages than those with uncontrolled epilepsy, who also more often receive a polytherapy and higher lamotrigine doses. This suggests that there might be a ceiling effect in the range of concentration exposure associated with seizure remission, as there was no patient in remission with blood levels higher

Table 1
Shows all patient's details, lamotrigine dosage and level, ns: non-significant.

	Total	Ongoing seizures	Remission	p, test used
Number	93	83 (89%)	10 (11%)	
Age (median, range)	50 (17–92)	49 (17–92)	57 (19–85)	ns
Gender (female)	47 (50%)	42 (49%)	6 (60%)	ns
Generalised epilepsy	25 (26%)	23 (28%)	2 (20%)	ns
Focal epilepsy	61 (64%)	54 (65%)	7 (70%)	ns
Polytherapy	48 (52%)	48 (58%)	0	<**0.0001** (Fisher's exact)
Tritherapy and more	11 (12%)	11 (13%)	0	0.6 (Fisher's exact)
Lamotrigine oral dosage (mg)				
Median	250	300	175	**0.028** (Mann–Whitney)
Range	25–1200	25–1200	50–300	
Mean	280.11	292.77	175	0.064 (Student t)
Standard deviation	189.84	195.24	85.80	
Lamotrigine serum level (mg/l)				
Median	4.87	5.39	2.33	**0.008** (Mann–Whitney)
Range	0.7–18.2	1.1–18.2	0.7–8.2	
Mean	5.83	6.16	3.10	**0.024** (Student t)
Standard deviation	4.06	4.11	2.37	

Values in bold are significant.