Clinical and Biological Assessment of Lamotrigine and Levetiracetam Plasma Assays at the Rennes University Hospital

B Le Daré[1], A Degremont[2], E Polard[3], I Morel[4], A Biraben[5], T Gicquel[4]

Affiliations

[1]Forensic Toxicology Laboratory, Rennes University Hospital, 35000 Rennes, France; Regional pharmacovigilance center, Rennes University Hospital, 35000 Rennes, France; Inserm, INRA, Institut NuMeCan (Nutrition, Metabolism and Cancer), Université Rennes, CHU de Rennes, 35000 Rennes, France. Electronic address: brendan.le.dare@chu-rennes.fr.

[2]Regional pharmacovigilance center, Rennes University Hospital, 35000 Rennes, France; REPERES department, Rennes University Hospital, 35000 Rennes, France.

[3]Regional pharmacovigilance center, Rennes University Hospital, 35000 Rennes, France.

[4]Forensic Toxicology Laboratory, Rennes University Hospital, 35000 Rennes, France; Inserm, INRA, Institut NuMeCan (Nutrition, Metabolism and Cancer), Université Rennes, CHU de Rennes, 35000 Rennes, France.

[5]Neurology department, Rennes University Hospital, 35000 Rennes, France.

Abstract

Introduction: Requests for lamotrigine and levetiracetam plasma assays have increased significantly since their development in the biological and forensic toxicology laboratory at the University Hospital of Rennes in 2015. The purpose of this study is to evaluate the follow-up of HAS recommendations for antiepileptic drug assays and the impact of assay results on the medical management modification.

Methods: Two hundred and forty-two assay results of these two antiepileptics were retrospectively analyzed in 169 patients hospitalized in different care departments between 2015 and 2018.

Results: The mean age of the study population was 50.3 years (+/- 25.4 years). Of the 207 assays prescribed for epilepsy, 177 (85.5%) were in line with the 2007 HAS recommendations, namely: 76/177 (42.9%) for therapeutic adjustment in the event of seizure recurrence or aggravation; 45/177 (25.4%) for specific clinical situations; 23/177 (13%) for proven or suspected poor compliance; 23/177 (13%) for suspected overdose; 8/177 (4.5%) following initiation of treatment; and 2/177 (1.1%) for drug interaction management. Thirty of the 207 assays (14.5%) were thus not recommended. No significant differences were found between patients with lamotrigine and/or levetiracetam plasma assays in therapeutic ranges and those with concentrations outside the therapeutic ranges, regarding the hospitalization frequency after a visit to the emergency room (p=0.9). Dosage changes were more frequent in patients with assays in therapeutic ranges compared to patients with plasma assays outside the therapeutic ranges (p=0.0015), suggesting a treatment reassessment primarily based on clinical criteria.

Conclusion: The request analysis for antiepileptic drug assays at the University Hospital of Rennes reveals that clinicians are well aware of the HAS recommendations. In addition, the assay results are mainly consistent with clinical intuition, suggesting a real added value in the patient management. However, the consequences on medical care seem limited. This assessment illustrates the importance of strengthening the dialogue between pharmacists, biologists and clinicians.

Keywords: antiepileptics, plasma assays, levetiracetam, lamotrigine, therapeutic management.

1. Introduction

Epilepsy is defined as a brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition. The definition of epilepsy thus requires the occurrence of at least one epileptic seizure (1). In France, the Haute Autorité de Santé (HAS) or French National Authority for Health estimates the number of people with epilepsy at 500,000 (2). The management of this pathology is mainly based on pharmacological treatment, making it possible to reduce the seizures frequency or even eliminate them.

Some antiepileptic drugs may have disadvantages in terms of their pharmacokinetic profile, including polymorphic enzymes metabolization, numerous drug interaction, active metabolites, saturable metabolism, high plasma protein binding or enzymatic inducer properties (3,4). These characteristics expose patients to wide inter and intra-individual variations in plasma concentrations, thus impacting the treatment efficacy and tolerance. In order to optimize the management of patients treated with antiepileptic drugs, pharmacological follow-up may be performed under certain conditions. The indications recommended by the HAS concern: the initiation of full-dose antiepileptic treatment after a period of a few weeks; proven or suspected poor compliance; suspicion of overdose; therapeutic adjustment in the event of seizure recurrence or aggravation, drug interaction management; and specific clinical situations: pregnancy, metabolic failure, etc. (2). Despite these specific clinical situations for which an interest in the pharmacological monitoring of antiepileptics has been suggested, the data in the literature show varying results in terms of compliance with these recommendations. In a French prospective study performed in a tertiary center, 84% of 698 antiepileptic drug levels measurement had an appropriate indication according to French guidelines (5). Conversely, Affolter et al. (2009) showed in a retrospective study on 602 antiepileptic drug serum level determinations that less than half of them met the criteria for appropriateness, creating unnecessary costs (6). Lastly, Kozer et al. concluded in 2003 that the results of plasma antiepileptic drug assays performed in pediatric emergencies were not associated with the resulting management (7).

In view of lamotrigine and levetiracetam plasma assays increasing requests at the University Hospital of Rennes (Brittany, France), we have carried out an evaluation of these practices. The objective of this work was to evaluate the follow-up of HAS recommendations, and the impact of assay results on medical management modification.

2. Material and methods

This retrospective observational study was conducted on 169 patients whose samples were returned to the biological and forensic toxicology laboratory at the University Hospital of Rennes between 2015 and 2018. Two hundred and forty-two assays were analyzed: 158 of lamotrigine and 82 of levetiracetam according to the appendix.

The data were extracted from Synergy® (TD Control®) software, which provides the plasma assays results performed by tandem mass spectrometry (LC-MS/MS) at the University Hospital of Rennes.

The variables studied concerned emergency department or hospitalization department, the molecule, the antiepileptic drug indication, the reason for prescribing the assay, the assay result, the age of the patient, and the consequences on the patient management, i.e. dosage changes, stopping or adding drugs, and the hospitalization frequency after a visit to the emergency department. These variables were collected from each patient's medical record (DxCare® Software, version 7.7.3). Considering that the time of the last intake of the drug was not indicated in these assays requests, we did not take into account the time of sampling. The consequences on medical management, analyzed by considering all the clinical situation (reason for admission in emergency department, addition or suppression of another drug, pregnancy, pathologies different from epilepsy), were compared between patients with plasma concentrations of antiepileptics in or outside therapeutic range. Based on data from the literature, the therapeutic range of 2 to 15 mg/L was selected for lamotrigine, and 6 to 40 mg/L for levetiracetam (8).

Figures and statistical analyses were performed using GraphPad® software (version 5.0, La Jolla, CA, USA). The variables were described using the usual parameters, namely mean and standard deviation for quantitative variables (age and plasma concentration) and frequency for qualitative variables (molecule, indication, hospitalization frequency, and medical management changes). Some parameters were compared in percentages using a Chi^2 Test between the population in the therapeutic range and the population outside the therapeutic range.

3. Results

3.1 Characteristics of assay requests

The assay activity for levetiracetam and lamotrigine began at the Laboratory of Biological Toxicology of the University Hospital of Rennes on 11/12/15 and 29/12/15 respectively. In 2016, these two molecules represented 33 assays, compared to 136 in 2018; the activity increased 4.1-fold between these two years (Figure 1). A total of 242 assays of these two molecules were prescribed between 2015 and 2018. The mean age of the patients included in this study was 50.3 years (+/- 25.4 years).

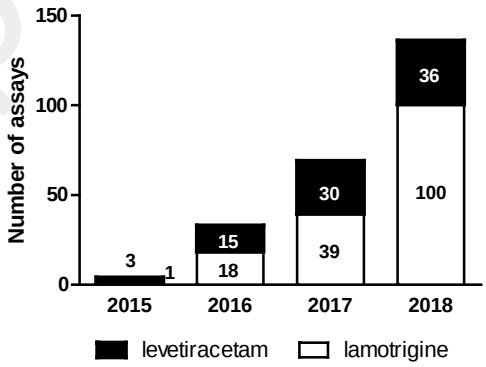

Figure 1 : Number of assays requests at the Laboratory of Biological and Forensic Toxicology at the University Hospital of Rennes for lamotrigine and levetiracetam determined by mass spectrometry (LC-MS/MS) from 2015 to 2018.

Of all the services that used a lamotrigine and/or levetiracetam assay, the five main prescribers, who prescribed approximately 72% of the assays, were in order of frequency: emergency departments (adults, pediatrics and gynaecology), intensive care units (medical and surgical), the long-term care unit (LTCU), the neurology department, and internal medicine / infectious disease departments.

3.2 Follow-up of HAS recommendations

Of all requests for lamotrigine and levetiracetam assays between 2015 and 2018 (N=242), 207 (85.5%) were prescribed for epilepsy; only 10 (4.1%) were requested for bipolar syndromes; and 25 (10.3%) had no reasons found. Due to the lack of data on assays in patients with bipolar disorder, these were not analyzed in this study (Appendix A).

Of the 207 assays prescribed for epilepsy, 177 (85.5%) were in line with the HAS recommendations, namely: 76/177 (42.9%) as part of a therapeutic adjustment in the event of seizure recurrence or aggravation; 45/177 (25.4%) for specific clinical situations (status epilepticus, pregnancy, postpartum, or acute renal failure); 23/177 (13%) for proven or suspected poor compliance; 23/177 (13%) for suspected overdose; 8/177 (4.5%) following initiation of treatment; and 2/177 (1.1%) for drug interaction management (Figure 2).

Thirty assays (14.5%) were out of HAS recommendations, finding 10 unexplained discomfort reports, six "other" reasons (treatment follow-up after a dosage change without seizure recurrence or aggravation, and assays after stopping treatment) and 14 (46.6%) assays for routine monitoring (Figure 2).

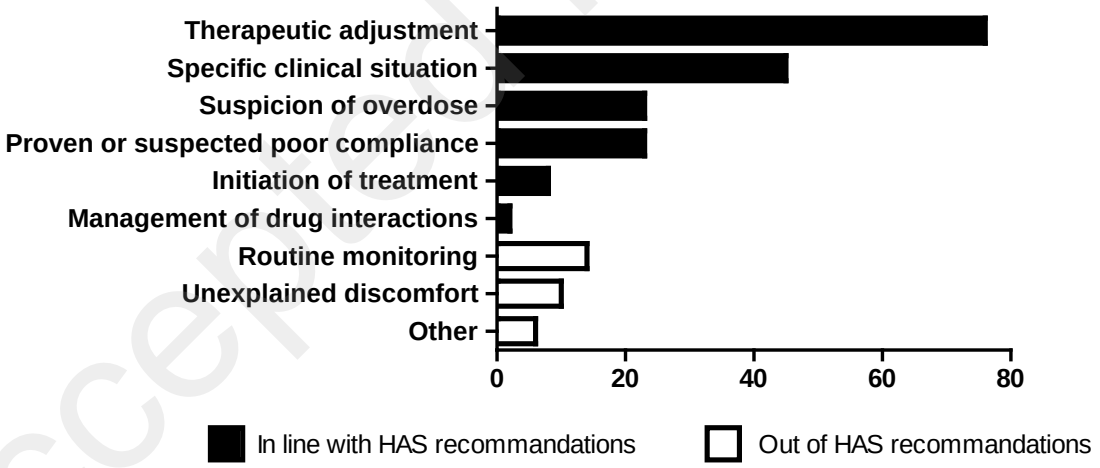

Figure 2 : Number of antiepileptic drug assays performed according to their reasons: in accordance with HAS 2007 recommendations (therapeutic adjustment, specific clinical situation, suspicion of overdose, proven or suspected poor compliance, initiation of treatment, drug interaction management) and excluding HAS 2007 recommendations (routine monitoring, unexplained discomfort, and Other (follow-up of treatment after dosage modification or not, without seizure recurrence)).

3.3 Results of the assays

In the case of lamotrigine or levetiracetam treatments in epileptic patients, approximately two thirds of the assays were found in the therapeutic range (89/137 (65%) and 46/70 (65.7%) respectively). In addition, lamotrigine and levetiracetam plasma concentrations showed a higher frequency of low plasma concentrations. Taken together, these results show that the majority of assays are located in the lower therapeutic ranges (Figure 3).

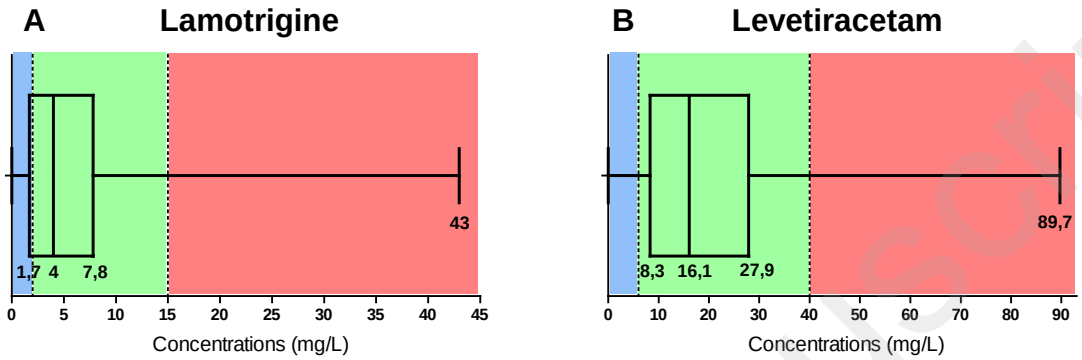

Figure 3 : Representation in a box and whisker plot of plasma concentrations (mg/L) of lamotrigine (A) and levetiracetam (B) in epileptic patients. The blue, green and red areas correspond respectively to underdose, results in the therapeutic range, and overdose.

Depending on the reasons for prescribing antiepileptic drugs, the proportions of underdose, assays in the therapeutic range and overdose are different (Figure 4). For assays performed as part of a therapeutic adjustment in the event of seizures recurrence or aggravation, the majority of plasma concentrations were found in the therapeutic range (Figure 4A). Considering the main specific clinical situations, in cases of status epilepticus, 19/29 (65.5%) lamotrigine and levetiracetam determinations found concentrations in the therapeutic range (Figure 4B). In the assays performed during pregnancy, 8/14 (57.1%) were below the therapeutic range, of which 6/14 (42.8%) were prescribed following iterative pregnancy vomiting (Figure 4C). For assays following proven or suspected non-compliance, 14/23 (60.9%) results were under-dosed (Figure 4D). In the context of suspected overdose, the results were 1/23 (4.3%) underdose, 14/23 (60.9%) doses in the therapeutic range and 8/23 (34.8%) overdose (Figure 4E). Epilepsy treatment initiation, when following an assay, found 6/8 (75%) plasma concentrations in the therapeutic range (Figure 4F). Assays for unexplained discomfort reports found 7/8 (87.5%) plasma concentrations in the therapeutic range (Figure 4G).

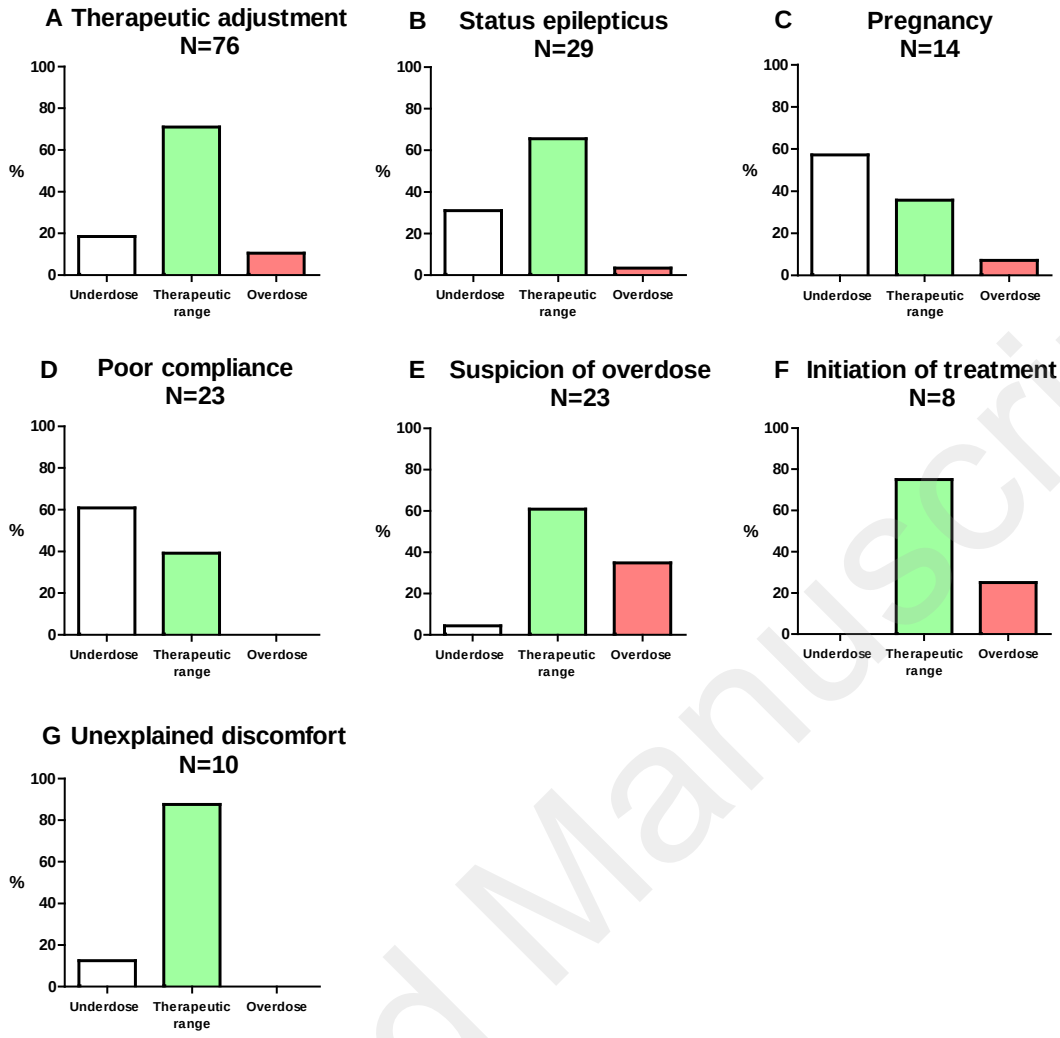

Figure 4 : Antiepileptic assay results expressed as a percentage of underdose, therapeutic range and overdose (levetiracetam and lamotrigine combined) according to the reasons for prescription: (A) Therapeutic adjustment in case of seizure recurrence or aggravation, (B) State of epilepsy, (C) Pregnancy, (D) Proven or suspected non-compliance, (E) Suspicion of overdose, (F) Initiation of treatment, (G) Assessment of unexplained discomfort.

3.4 Therapeutic management following the results of assays

Seventy six assays were performed in emergency departments, 28 were included in and 48 out the therapeutic ranges, the percentage of hospitalized patients were 53.6% (15/28) and 52.1% (25/48), respectively. No significant difference was found between patients with antiepileptic concentrations in and those outside therapeutic ranges regarding the rate of hospitalization (p=0.9) (Figure 5A).

Similarly, the dosage changes as well as the treatment changes were compared with the assay results for all prescribing services. Patients with plasma concentrations in the therapeutic ranges had more dosage changes (27.4% (34/124)) compared to those with plasma concentrations outside the therapeutic ranges (8.9% (7/78)) (p=0.0015). However, the background treatment change (discontinuation or addition of an antiepileptic drug) was not significantly different between these two groups (12.9% (16/124) and 7.7% (6/78) respectively) (p=0.247). The lack of change in

antiepileptic treatment (dosage modification, addition or discontinuation of treatment) was therefore more frequent when plasma concentrations were outside therapeutic ranges (83.3% (65/78) compared to 59.7% (74/124) when plasma concentrations were in therapeutic ranges) (*p*=0.0004) (Figure 5B).

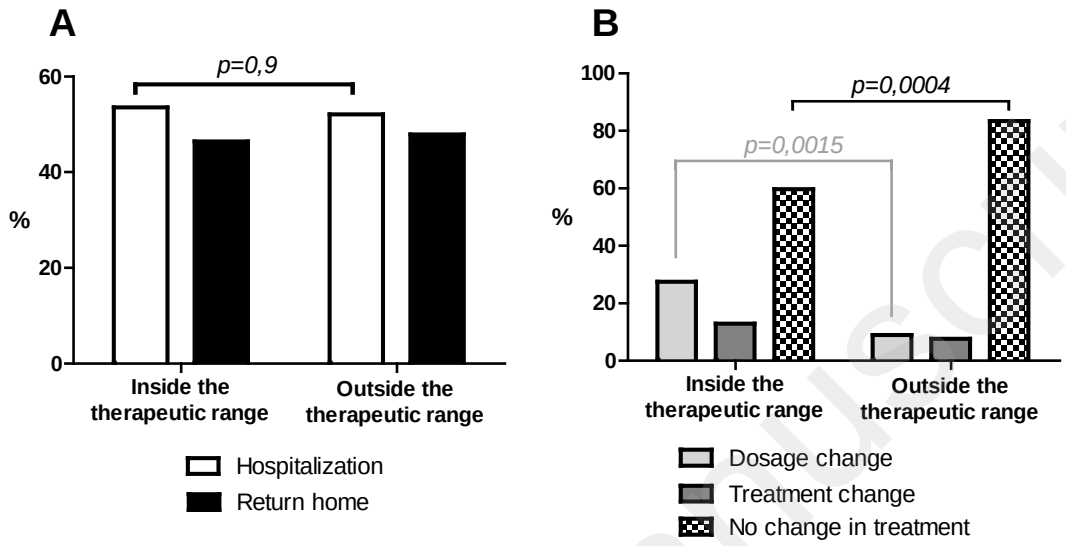

Figure 5 : Medical management based on the results of lamotrigine and levetiracetam assays. (A) Percentage of hospitalization and return home following a visit to the emergencies. (B) Percentage of antiepileptic dosage change, treatment change (discontinuation of antiepileptic +/- introduction of a new antiepileptic treatment) and no change in treatment.

4. Discussion

Of the 242 assays performed since 2015, the vast majority (N=207) are in epileptic patients on whom the analyses have been targeted. Patients with lamotrigine therapy associated with levetiracetam were included in each group, so the patient number is lower than the assay number. From a general point of view, it is interesting to note that the most prescribing services of these assays are the emergency, intensive care unit, LTCU and neurology departments. These results seem consistent, given the reasons for the assay recommended by the HAS (2). In our study, 85.5% of the assays were in compliance with the 2007 HAS recommendations, indicating that clinicians generally complied with them well (Appendix A).

The results of lamotrigine and levetiracetam assays according to the reasons for prescription show a strong consistency with clinical intuition. The clearest examples concerns proven or suspected poor compliance, for which the highest proportion of underdose is found (Figure 4D). While measurement for suspected overdose found a high proportion of overdose (40%), we also found a high proportion of assays in therapeutic range. Measurement performed for therapeutic adjustment also found the highest proportion of assays in the therapeutic range (Figure 4A). However, data from the literature defined therapeutic range as the range of drug concentrations that provide best achievable response in a given patient (9). Thus, a drug concentration considered in therapeutic standardized reference

range can be considered underdose or overdose in some individuals, explaining our findings. Here, the use of 6 to 40 mg/L as levetiracetam therapeutic range can constitute an overstatement of assays in therapeutic range, where the use of 12-46 mg/L therapeutic range according to Jacob and Nair (2016) would have found more underdose (10). This limitation could explain why only 20% of assays performed in case of exacerbation or resurgence of epileptic seizures reported sub-therapeutic concentrations.

Considering hospitalization as a criterion for the severity of the disease, it seems consistent that an assay outside the therapeutic ranges should not be associated with a decision to hospitalize. Furthermore, these findings must be interpreted in the context of two potential limitations. Firstly, the retrospective design limited available data to those reported by physicians. This implies that unexplained discomfort reports could have been related to clinical signs of overdose and therefore associated with assays for suspicion of overdose. Considering that the medical records did not mention it, we classified these cases as non-recommended indications. Secondly, it is not excluded that (i) before receiving the result, another cause may be found, leading the patient to an emergency exit and (ii) that all assays were not known before patients were hospitalized.

The percentage of dosage change is significantly higher when plasma concentrations are in therapeutic ranges (p=0.0015). The lack of change in antiepileptic treatment (dosage modification, addition or discontinuation of treatment) was more frequent when plasma concentrations were outside therapeutic ranges (p=0.0004). These results suggest a re-evaluation of antiepileptic treatment mainly based on clinical criteria. In the literature, Kozer et al (2003) conclude in a similar way, reporting that the antiepileptic drug assays outside a context of pharmacological therapeutic monitoring does not provide significant added value in practice and does not lead to a change in management in a paediatric emergency department (7). As Selim and Cichowski (2018) point out, a dilemma arises regarding the management of the often expensive and unreliable assay result, which in some cases leads to unnecessary dosage changes that may increase the risk of adverse reactions (11). In the case of persistent seizures, however, an assay may fall within the therapeutic range to assess the possibility of dosage increases. Here, we were limited by the lack of visibility on follow-up outside the hospital. It is therefore not excluded that treatment changes may have been made subsequently.

In the context of pharmacological therapeutic follow-up, the time of sampling, the patient's clinical condition, or the therapeutic ranges targeted by clinicians, are essential information for interpreting the result and therefore for customizing treatment (12). From an analytical point of view, good practices for the antiepileptic drugs determination recommend blood sampling just before the next oral dose, a condition in which the target concentrations have been defined (9). In the case of analyses requested by the intensive care and emergency services, the hospital context is rarely compatible with this condition and samples are taken at all times. This parameter constitutes a major bias in a result report alone, due to the lack of visibility on the drug pharmacokinetics, and makes it difficult to interpret the result. Consequently, the interest of these assays is limited here to the comparison of the patient's clinical condition with a plasma concentration at the same time, and therefore does not constitute a pharmacological therapeutic follow-up (10,12–14). However, despite the absence of the time of sampling, lamotrigine and levetiracetam assays remain relevant for this study, considering (i) that according to the levetiracetam monography, the maximal concentration at the steady state for 1000 mg twice a day is 43 µg/mL, and thus nearly included in the therapeutic

ranges and (ii) that lamotrigine elimination half-life is between 15h and 35h, showing a poor variation in plasma concentrations between two drug intakes when the steady state is reached.

This study highlights the difficulties encountered to obtain the information necessary for optimal care. Therefore, a relevant interpretation of the antiepileptic drug assays results in clinical practice remains difficult as it stands. These data reinforce the major interest of clinical-biological dialogue in optimizing individualized treatments and increasing its impact on medical care.

5. Conclusion

The requests analysis for antiepileptic drug assays at the University Hospital of Rennes reveals that clinicians are following HAS recommendations well. In addition, the assays results are mainly consistent with clinical intuition, suggesting a real added value in the patient management. However, the consequences on medical care seem limited. This assessment illustrates the importance of strengthening the dialogue between pharmacists, biologists and clinicians.

6. Conflict of interest

The authors declare no conflict of interest

7. Bibliography

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<u>Appendix A:</u> Flow chart representing the reasons for prescribing lamotrigine (LTG) and levetiracetam (LEV) assays, the number of assays that comply or not with HAS 2007 recommendations, and the number of assays per prescription reason.