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Therapeutic drug monitoring of newer generation antiseizure medications at the point of treatment failure

Paul Fluckiger [a], Irene Aícua-Rapún [b], Pascal André [c], Andrea O. Rossetti [b], Laurent A. Decosterd [d], Thierry Buclin [c], Jan Novy [b,*]

[a] Bachelor of Medicine, University of Lausanne, Switzerland
[b] Department of Clinical Neurosciences, Neurology service, Lausanne University Hospital (CHUV) and University of Lausanne, Switzerland
[c] Service of Clinical Pharmacology, Lausanne University Hospital (CHUV) and University of Lausanne, Switzerland
[d] Laboratory of Clinical Pharmacology, Lausanne University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland

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ABSTRACT

Purpose: The benefit of therapeutic drug monitoring (TDM) of newer generation antiseizure medications (ASM) has been little studied. A recent randomized study suggested that TDM at each medical visit did not bring a significant benefit, but the study did not investigate TDM in cases of treatment failure. Accordingly, we realized a *post hoc* analysis of this trial.
Methods: We analyzed 282 TDMs in 136 patients. We compared TDM performed at visits after treatment failure versus without treatment failure, reporting the proportion of drug levels out of range and the prescriber's adherence to dosage recommendations according to measured drug levels.
Results: There was no statistical difference in terms of proportion of out of range plasma drug levels (47% vs 50%, $p = 0.7$) or adherence of prescribers to the clinical pharmacologists' dosage recommendations (21% vs 30%, $p = 0.6$) between visits after treatment failure and visits without treatment failure, respectively. Knowledge of prior drug levels did not modify the results.
Conclusion: Systematic TDM at appointments following treatment failure showed similar results to TDM at visits without treatment failure. The prescribers' adherence with dosage recommendations was low in both cases. It is not clear whether better prescriber adherence would improve patient outcome. Furthermore, the ability to detect poor patient compliance is limited in a planned outpatient appointment. The study setting does not reflect on the general usefulness of TDM.

1. Introduction

Therapeutic drug monitoring (TDM) of older generation antiseizure medications (ASMs) such as phenytoin, carbamazepine, phenobarbital or valproate has been widely used since 1960 and the relationship between plasma ASM levels and a clinical effect was well established for some of these agents [1]. Pharmacokinetic characteristics such as non-linear metabolism or drug-drug interactions support the use of TDM for this type of medication. Prescription of older agents however, is decreasing in favor of newer generation ASMs (i.e. lamotrigine, levetiracetam, oxcarbazepine, topiramate, pregabaline, zonisamide, lacosamide, perampanel, brivaracetam) [2]. While the newer ASMs induce less drug-drug interactions, they still have high inter-individual pharmacokinetic variability [3, 4].

The use of TDM regarding newer generation ASMs has received little attention; the international league against epilepsy (ILAE) established recommendations for TDM use [5]. We recently reported our randomized controlled trial showing that systematic TDM of newer generation ASMs in patients with epilepsy appeared unlikely to bring tangible benefits to clinical practice when compared to TDM performed only at treatment failure [6]. The trial showed no benefit of TDM in preventing treatment failure but did not assess TDM at the moment of treatment failure. We could argue that while plasma drug levels may not be crucial for routine follow-up, they may be more valuable at treatment failure to guide the changes needed at this time.

The aim of this study is to explore TDM when ASM therapy fails,

; TDM, therapeutic drug monitoring; ASM, Antiseizure medication.

* Corresponding author at: Service de Neurologie BH07, CHUV, Rue du Bugnon 46, 1011 Lausanne, Switzerland.
E-mail address: jan.novy@chuv.ch (J. Novy).

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assessing if TDM shows out of range drug levels more frequently, and how clinicians use TDM results.

2. Materials and methods

We performed a *post hoc* analysis of our previously reported prospective TDM trial of newer generation ASMs [6]. We conducted this single center trial at the Lausanne University hospital (CHUV) between June 2016 and December 2018. The trial included patients with epilepsy requiring either the introduction or modification of a treatment regimen with lamotrigine, levetiracetam, zonisamide, oxcarbazepine, topiramate, lacosamide, pregabalin, brivaracetam or perampanel. We also monitored older generation ASMs. The study included two arms: a "systematic" arm, in which plasma medication levels were systematically communicated to the treating clinician and a "rescue" arm, in which plasma levels were only available if the treatment had failed. We pre-defined treatment failure by a composite endpoint (occurrence of status epilepticus, $\geq$ 2 seizures with loss of awareness in the one-year follow-up period, need to add-on another ASM or need to discontinue the study drug because of poor tolerability). Clinical pharmacologists reviewed all drug levels and recommended corresponding dosage adjustments. Clinicians were free to adjust the medication as judged necessary in both arms, in the systematic arm with knowledge of the plasma drug level and recommended dosage adjustment. The final visit either occurred at the one-year follow-up or after the participant reached one of the endpoints (treatment failure). We recorded any treatment changes at each visit, including the visit meeting the treatment failure endpoint.

We assessed the proportion of drug plasma levels outside of the reference range and the prescriber's adherence to the dosage recommendations of the clinical pharmacologists (i.e. whether the treating physician modified the treatment according to drug level information or not). We considered plasma levels (performed at least 6 h after the last dosing) as outside the reference range if they were above or below the ranges defined by the ILAE [5, 7]. In patients on several medications, we calculated the proportion of drug levels outside the reference range for each drug. We compared collected variables from visits where treatment failure had occurred (final visits) with visits without treatment failure (i.e. final visit without treatment failure or penultimate visit for patients with treatment failure). We defined prescriber adherence to dosage recommendations as clinicians adjusting the treatment dosage of a medication with plasma levels outside of the reference range (as defined by the ILAE [5, 7]) with the aim of reaching the reference range (see figure 1). For patients on several medications, we calculated the proportion of the adherence (overall adherence). If a patient with multiple ASMs had to discontinue one of them, we calculated the prescriber's adherence to dosage recommendations of the continued ASMs. We also compared collected variables from systematic arm where previous drug levels were known with the rescue arm where previous drug levels were not available to the clinicians until treatment failure.

We further assessed if a significant drop in plasma medication level (>50%) was associated with treatment failure. Such a drop is considered significant as it is unlikely to be explained by a spontaneous variation in the drug level, and can be interpreted as poor compliance if there is no other explanation [8]. We compared drug levels at visits without treatment failure to visits with treatment failure and considered that a 50% drop happened if any of the levels measured in a polytherapy showed such a decrease.

For univariable analyses, we used Mann–Whitney U or χ^2 test as needed. P values <0.05 were considered as significant. We used R 3.6.3 software (R Core Team 2020).

3. Results

Among participants included in the previous study [6] ($n = 151$), we excluded those without available medication levels for the last two visits ($n = 15$). Of the 136 patients included, 130 patients had measured drug levels at the penultimate visit and 59 patients at the final visit, of which 44 (75%) had treatment failure (a proportion of patients without treatment failure did not have drug level measures at the final visit, having stopped their medication before that visit).

Table 1
Characteristics of the cohort.

	Overall (n = 136)	No treatment failure (n = 82)	Treatment failure (n = 54)	p-value	Test
Gender (male) (n(%))	58 (42.6%)	32 (39%)	26 (48.1%)	0.381	χ^2
Age (median [range])	37 [18, 82]	40 [18, 82]	32 [18, 81]	0.024	Mann-Whitney U
Generalized epilepsy (n (%))	34 (25%)	19 (23.2%)	15 (27.8%)	0.686	χ^2
Epilepsy duration (median [range])	7 [0, 47]	5 [0, 47]	13 [0, 47]	**0.001**	Mann-Whitney U
Monotherapy (n(%))	72 (52.9%)	54 (65.9%)	18 (33.3%)	< **0.001**	χ^2
ASM tried before (median [range])	1 [0 - 9]	1 [0 −7]	1 [0 - 9]	0.283	Mann-Whitney U
Drug resistant epilepsy (n (%))*	67 (49.3%)	39 (47.6%)	28 (51.9%)	0.753	χ^2

* Defined as ≥2 adequate ASM inefficacious [21].
Bold values are significant after Bonferroni correction.

We considered 282 medication levels of 189 visits. Patient details can be found in table 1. ASMs were distributed as follows: lamotrigine (in 66 participants), levetiracetam (31), zonisamide (20), valproate (15), pregabaline (11), topiramate (9), lacosamide (6), brivaracetam (5), carbamazepine (5), oxcarbazepine (4), perampanel (4) and rufinamide (2). After correcting for multiple testing (Bonferroni), longer disease duration and polytherapy were associated with a higher likelihood of treatment failure during the study follow-up. Treatment inefficacy alone accounted for the majority of treatment failure (63%), followed by combined inefficiency and toxicity in 28% and toxicity in 9%.

Overall, 52% of plasma drug levels were within the reference range, while the vast majority of the "out of range" plasma drug levels (132/134) were below the reference range. Five patients had undetectable levels of at least one ASM in the visits considered in this study. There was no difference regarding the proportion of treatment failure between patients with undetectable plasma drug levels (40%) and those with detectable drug levels for all their medications (39.7%) ($p = 0.995$, Mann Whitney U). There was no statistically significant difference in terms of the proportion of drug levels outside the reference range for visits where treatment had failed (median: 50%, 0–100%) compared to visits without treatment failure (50%, 0–100%, $p = 0.664$, Mann Whitney). Considering patients on lamotrigine only, there was no significant difference in the proportion of levels outside the reference range in visits without treatment failure (25/61, 40.9%) in comparison with visits with treatment failure (5/16, 31%, $p = 0.57$, Fisher exact test).

Considering patients with a drop of 50% in medication levels at the final visit (for at least 1 ASM), 14/19 (73%) had reached an endpoint and those without this decrease reached an endpoint in 23/31 (74%, $p = 0.97$, chi squared) of cases. When considering only the inefficacy endpoint, results were not different (10/19, 52% vs 18/31, 58%, $p = 0.7$, chi squared).

When analyzing a prescriber's adherence to dosage recommendations, we excluded ASMs that the treating clinician chose to discontinue; indeed, it was difficult to assess if TDM was followed if medication was

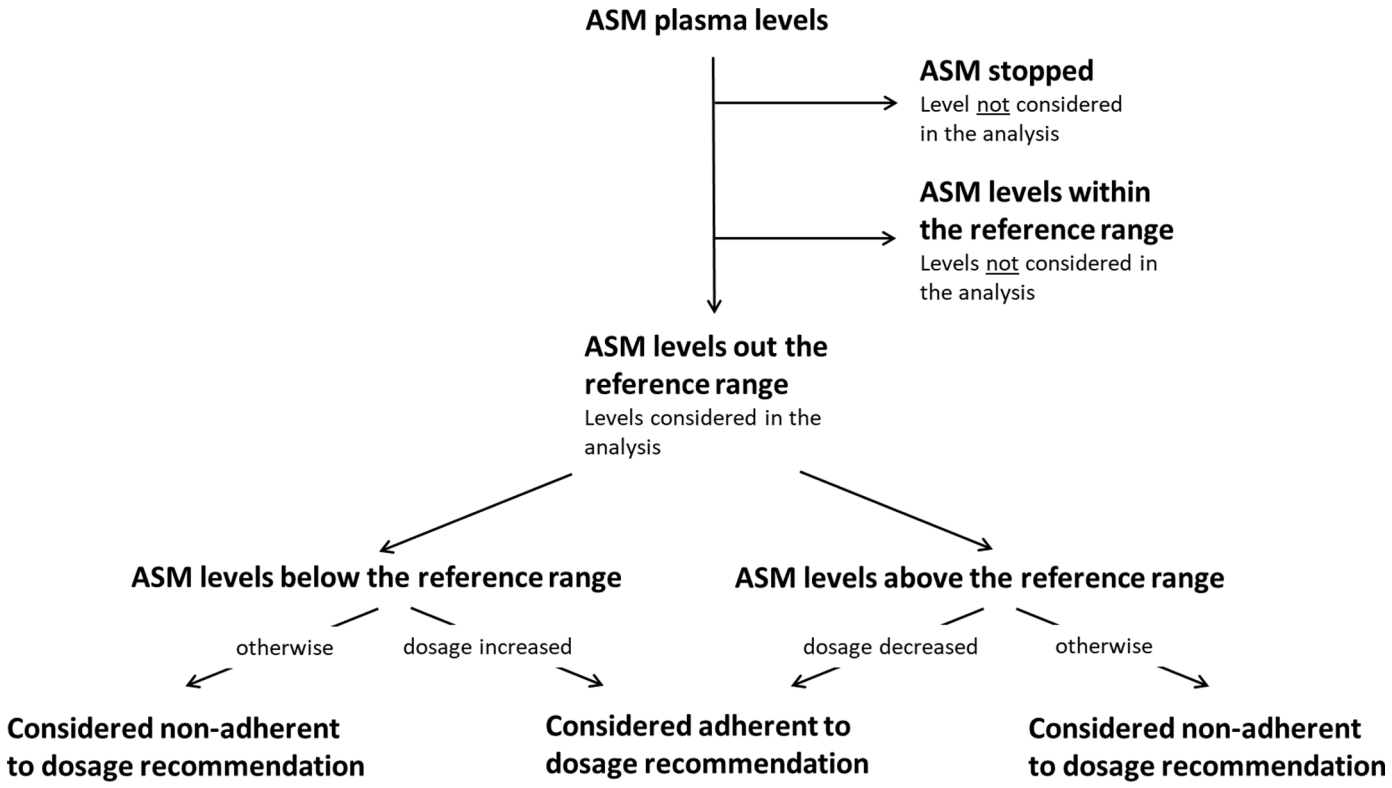

Fig. 1. Determination of prescriber adherence to dosage recommendations proposed by clinical pharmacologists.

discontinued for tolerability reasons: If the TDM indicated increasing medication dosage in case of inefficacy supported by low drug levels, following this advice would be impossible if the treatment was associated with adverse events at the current dosage. We analyzed only levels outside of the reference range. Prescribers' adherence to dosage recommendations for 123 medication levels was 23% overall. Figures were similar for visits where treatment had failed (mean: 21%, range: 0–100%) and for visits without treatment failure (mean: 30%, range: 0–100%) ($p = 0.569$, Mann Whitney). There were no cases of decreasing treatment dose due to plasma levels above the reference range (to reach the reference range) without any adverse events. TDM at treatment failure without a prior knowledge of medication levels did not result in increased prescriber adherence to dosage recommendations, compared with the visit with previously available TDM (mean 21%, range 0–100% vs. mean 45%, range 0–100%, $p = 0.223$ Mann Whitney) (Fig. 1).

There was no significant difference in any of the above results if we stratified the endpoints by inefficacity (status epilepticus, ≥ 2 seizures with loss of awareness during the one-year follow-up, need to add-on another ASM) or tolerability (need to discontinue the treatment).

4. Discussion

Our results show little difference regarding plasma drug levels or prescribers' adherence to dosage recommendation at visits where treatment was considered to have failed and visits where it had not failed. We did not find the nature of the failure (mostly inefficacy) or prior knowledge of the patient's plasma levels to be confounders. These results suggest that there is a limited benefit in performing systematic monitoring of newer generation ASM plasma levels in the outpatient clinic if treatment fails; however, the specific context of the study has important consequences on the results. Treatment failure was in the vast majority of cases due to insufficient seizure control. In this case, an invaluable input of TDM is to ascertain the patient's exposure to the treatment, thereby detecting short-term poor compliance [9]. The possibility of discerning non-compliance at a planned appointment is however, much lower than when TDM is performed directly following the occurrence of breakthrough seizure. Patients are indeed much more likely to take medication before attending an appointment [10], especially if they experienced a recurrence. This effect is often called the "tooth brush" effect in reference to people brushing their teeth more assiduously in the days before their dentist appointment. Overt non-compliance (undetectable drug levels) in the setting of our study was very uncommon. We may also wrongly assume that plasma drug levels below the reference range are a sign of poor compliance, there are several explanations for low levels (patients who are rapid metabolizers or liver enzyme induction). Moreover, low plasma medication levels are often found in long-term seizure freedom [11], as patients responding to treatment often do so at low dosage [12].

Prescribers' adherence to dosage recommendation in relation to out-of-range levels was generally low, which raises the issue of the practical use of TDM. Several points might limit the direct transcription of TDM results into clinical practice. Adverse events can occur at any drug concentration, which may hinder a clinician's ability to titrate medication further to reach the reference range in case of insufficient efficacy. Reference ranges are levels at which efficacy and acceptable tolerability are most likely, but there is wide inter-individual variability. Indeed, several studies showed that seizure freedom is achieved at low dosage [13, 14], and consequently at low levels [15]. From these observations, some clinicians might infer that for a failing treatment, detectable plasma ASM levels with large margins but below the reference range, would call for ASM switching or adding rather than increasing the dose. Similarly, absence of any benefit or even worsening during ASM titration may lead clinicians to switch medication rather, even if medication levels may not have reached the reference range, as prospects of a satisfactory outcome seem unlikely. Limited adherence of clinicians to TDM dosage recommendations of clinical pharmacologists has been a matter of debate for a long time, and already highlighted [5] about the first trial on TDM of older ASMs [16]. In the trial analyzed here, we did not find an effect of clinicians adherence to TDM [6], but in other fields such as TDM in oral targeted anticancer therapy with

imatinib, this was the case [17]. A major limitation of the use of TDM for newer generation ASMs (the vast majority of the treatments used in this study) is less experience in the interpretation of plasma drug levels with less well-defined standardized reference ranges for these medications in comparison with older generation ASMs [7]. For this reason, we expressed TDM interpretation in terms of recommendations and clinicians remained free to follow the recommendations or not. The use of individual therapeutic ranges has been advocated to address the limited correlation between clinical effects and standardized reference ranges [18]. However, individual therapeutic ranges are much more difficult to study, as they require repeated measures to identify concentration ranges correlated with a satisfactory treatment effect for each patient. Individual ranges are therefore of little help when titrating a new medication. In addition, outcome is likely to be heterogeneous for individual therapeutic ranges, also a major limitation. Some patients may be seizure free while others may experience quantitative or even only qualitative improvement of their seizures.

Our results do not indicate that TDM is not useful altogether. There are several situations in which TDM is invaluable (e.g., in pregnancy [19], for drug interactions, suspected toxicity or noncompliance) and clearly recommended [5, 7] as pharmacokinetic interactions or changes cannot be demonstrated otherwise. In addition, TDM studies informed on how to handle ASM combination therapy effectively. The use of newly released ASMs also warrants caution concerning drug-drug interactions, and TDM assists clinicians in this setting.

This study has several limitations. The original trial was not designed to assess the long-term benefit of TDM *after treatment failure* and as such advises only on the use of TDM after treatment was considered to have failed. There was no control group of treatment failure without TDM and therefore, we could not assess the lack of TDM at treatment failure. In the original study, we assumed that an endpoint was a one-off event and so considered that no patient reached an endpoint at the penultimate visit. This allowed to define treatment failure easily but could distort results if the endpoints were rather final states that deteriorated over time. This latter definition is likely to represent at least some situations, such as incomplete seizure control that may be regarded at some point as treatment failure. Intervals between visits were irregular as the original trial was as pragmatic as possible to reflect the clinical practice. The original trial aimed to assess the general usefulness of TDM and excluded some groups that could more obviously benefit from TDM, for instance pregnant women, or intellectually disabled patients who could not give consent. Certainly, we cannot infer the relevance of TDM at treatment failure in these groups from the data. We considered the ASMs here as a whole, overlooking that TDM of some ASMs (such as lamotrigine) might be more useful than that of others [20]. Our results on lamotrigine however, did not show different trends compared to ASMs taken as a whole.

Systematic TDM at appointments following treatment failure showed similar results to visits without treatment failure. Prescribers' adherence to dosage recommendations was low in both cases. It is not clear whether better prescriber adherence might improve patient outcomes.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2021.11.022.

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