Individualized therapeutic levels: Adequate use of antiepileptic drug monitoring

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Abstract

Therapeutic monitoring of antiepileptic drug plasma levels is an important tool in the management of epilepsy, but it needs to be applied intelligently, as it otherwise can easily become counterproductive. The present article discusses the significance of low, average and high reference ranges, and typical mistakes derived from their misunderstanding (dose decrease in perfectly well-treated patients because of a high level; unnecessary dose increase in seizure free patients because of low levels; failure to increase dose in uncontrolled patients because of a level "in the therapeutic range"). "Therapeutic range" should never be applied in general but only with respect to individual patients. The necessity is highlighted of establishing an individual therapeutic level as a reference for all later issues that might arise. Aspects of particular practical importance such as the role of plasma levels for the assessment of adherence and the establishment of pharmacoresistance are discussed in more detail.

KEYWORDS: NON-ADHERENCE – PHARMACORESISTANCE – ENZYME-INDUCTION – REFERENCE RANGES – BREAKTHROUGH SEIZURES – SEIZURE CONTROL – ANTIEPILEPTIC DRUG TOXICITY

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Introduction

For the vast majority of patients with epilepsy, pharmacotherapy with antiepileptic drugs (AED) is the treatment of choice. It is a treatment that requires considerable expertise since many drugs are available but not all are suitable for everybody and, unlike many other medical conditions, there is no standard dosing[1]. In addition, AED pharmacokinetics (PK) are variable with the consequence that, with many AEDs, it is not sufficient to look at doses but primarily to consider AED plasma levels (PL). These are raw numerical values that need an interpretation. To help with this, practically all laboratories send their results together with reference ranges. These are based on cohort statistics where most successfully treated cases without serious side effects are found in the middle range. It is therefore often called the "therapeutic range" which can easily be misunderstood. Treatment above this range carries an increased risk of toxicity and therefore needs more attention. Some patients can successfully be treated at lower levels, which is optimal with respect to side effects. The term "therapeutic level" should only be used with respect to individual cases.

Reference ranges are often misunderstood as normal ranges, which may have serious consequences. They really only give a rough indication if the patient is on a high, average or low dose but do not tell in what range the individual patient's treatment should be kept.

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Individually, the optimal plasma level is the lowest level at which the patient is seizure free without unacceptable side effects.

In this article, we discuss various aspects of the correct and incorrect utilization of AED levels. Some important principles are presented in table 1.

Table 1: Basic rules for therapeutic AED monitoring

Some rules should always be applied with therapeutic drug monitoring (TDM) of AEDs.

TROUGH LEVELS: For many AEDs, the PLs fluctuate during the day dependent on intake and metabolism. Therefore, PLs taken at different hours during the day are not reliably comparable. One of the most stable levels, and easiest to organize, is the level before the first dose of the day, the "morning trough level". It is advisable to use this PL as a standard.

TOXICITY: An exception from this rule is a patient complaint suspicious of dose-dependent side effects of a drug with a short half-life whose PLs are likely to fluctuate (such as carbamazepine). In this case, the morning trough level is often misleading and, to decide if there is toxicity, the blood specimen needs to be taken at the time when the complaints are most prominent.

STEADY STATE: PLs should only be determined when the drug can be expected to be in a "steady state" where intake and excretion are in full balance. As a rule of thumb, this is the case after approximately 5 half lives of the drug.

ICTAL PL: Again, there is an exception from this rule which is the clarification of a breakthrough seizure in a patient who should be seizure free. In this case, we are not interested in the steady state but in the immediate postictal PL to see if it deviates from the pre-established steady state.

High plasma levels

Some AED labs designate the range above the average span as the "toxic range". This is misleading because, although in this range there is an increased risk of toxicity, by no means all patients experience it. In fact, with levels little above the average range, only few patients show toxic symptoms or signs. On the other hand, some patients with a high seizure propensity only remain seizure free on the condition to have higher than average PLs, and their regimen needs to be maintained there. If they have no serious side effects this is no problem. If they do have side effects, they are resistant to this drug and it needs to be changed.

Patients on treatment with high levels require increased attention so the development of side effects is not overlooked. Regular PL monitoring may be recommendable so further increase of PLs is not missed. This is particularly true for a drug with non-linear PK such as phenytoin where e.g. moderate weight loss may produce a substantial increase resulting in toxicity.

POSSIBLE MISTAKE: to reduce the AED dose because of a high level when there are no clinical signs of overdose. In seizure free patients with a high individual therapeutic level this will almost invariably produce a seizure relapse with possibly deleterious consequences.

Low plasma levels

Some labs designate the range below the average span as the "subtherapeutic range". This is misleading because patients with a low seizure propensity need no higher levels to reach full therapeutic success. For them, the low PL is the therapeutic PL.

There are many reasons why a patient can have a low PL of an AED, for example:

- Deliberate low-dose treatment (because of full success; to avoid side effects)
- Co-medication with enzyme-inducing drugs (AED or other)
- Non-adherence with treatment (see below)
- Reduced absorption
- Rapid metabolization (genetic enzyme polymorphism)
- Pregnancy

In seizure free patients, low PLs are no concern at all. If seizures persist, the dose needs probably to be increased. If the low PL coincides with a breakthrough seizure it needs to be compared with the patient's previous levels. If there was a fall in PL, the reason must be investigated and corrected. Typical reasons are non-adherence; PK interaction with co-medication; preparation shift[2]; or intermittent illness

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(febrile or not). Regarding co-medications, the patients need to be expressedy asked as they may include some over-the-counter medicines, teas, vitamins etc. Patients should be instructed that, if vomiting occurs and the tablets are visible, the entire last dose needs to be taken again. If no drugs are in the vomit and more than one to two hours have passed after intake, the drugs have probably been absorbed. In case of doubt, if the individual therapeutic PL is on the low side, it is safe to repeat the whole dose, otherwise the half dose.

In health systems where medicines are not provided for free, patients with PLs below expectance may have missed doses because they could not afford the drug. This needs to be enquired in a regardful way, not to make them ashamed of their condition.

POSSIBLE MISTAKE: to increase the AED dose in a seizure free patient because of a low PL. This is not particularly dangerous, but absolutely meaningless. Nobody should receive more medicine than necessary; it increases the risk of dose-dependent side effects, particularly in elder and multimorbid patients treated with multiple drugs. It also is a waste of money. It is especially counterproductive for patients with longstanding seizure control who are in the stage of stepwise AED taper.

Average plasma levels

Some labs designate the average range as the "therapeutic range". This is grossly misleading because a PL somewhere within this range by no means guarantees full therapeutic action. If the patient continues to have seizures, dose and PL need urgently to be increased. As long as the PL remains in the average range there is little risk of side effects. An average PL also does not prove that the patient is fully adherent to the prescribed treatment[3].

POSSIBLE MISTAKES: to keep treatment unchanged although the patient's seizures continue because the PL is "within the therapeutic range"; to consider this patient as resistant to this drug is a classic example of pseudo-pharmacoresistance.

Individual therapeutic level

Epilepsy is a very variable condition where individual patients differ strongly with respect to seizure propensity. There are mild epilepsies where the seizure propensity is only slightly elevated above normal (even normal brains have some seizure propensity). They need only low-dose treatment. At the other end of the spectrum, there are severe epilepsies where the seizure propensity is so high that it cannot be fully outbalanced by AEDs. It makes no sense to talk about "therapeutic levels" in general. In mild epilepsies, the therapeutic level is low whereas the severest epilepsies have no therapeutic level at all; they are pharmocoresistant.

The individual therapeutic PL cannot be predicted but is found empirically. Typically, AED treatment begins with adjustment to a moderate first target dose. If the patient becomes seizure free, the PL of this dose is considered the therapeutic level. If seizures continue, dose is increased to a higher tentative therapeutic level. This continues until the patient becomes seizure free with a dose and level, which is the patient's definite therapeutic PL. However, if the last increment produces dose-dependent side effects the patient is resistant to this drug, which should be replaced by another.

When can a patient be considered seizure free? The recommendation by the International League against Epilepsy in view of defining pharmacoresistance[4] stipulates a period of at least 3 times the longest pre-intervention inter-seizure interval or 12 months, whichever is longer. For dose-finding in AED treatment this definition is only moderately helpful. If a patient had several seizures a week and they stop with a new treatment, after a month without seizures there is good reason to hope that the effect will last; the dose will be maintained and a tentative therapeutic PL can be determined. But if a patient only had 2-3 seizures a year, one year without seizures does not suffice to consider him seizure free. However, the decision after one year will be again to measure the PL, keep the AED dose unchanged and see what happens. In this case, it is more likely that the tentative seizure freedom will not hold and the dose and PL will need adjustment. Therefore, to find the individual therapeutic levels often takes longer when seizures are rare than when they are frequent.

Once the individual therapeutic PL is established it serves as a reference for comparison with all later levels that are determined to clarify possible toxicity, breakthrough seizures and whatever other treatment-related question.

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Adherence

Non-adherence with the prescribed treatment is a frequent problem of AED treatment and a common cause of treatment failure. Therefore, it is important to recognize and prevent it, and PLs can be helpful if utilized correctly. An isolated low PL does not indicate non-adherence as it may have many possible causes (vide supra). Lunardi et al[3] studied a cohort explored for possible epilepsy surgery where they monitored PLs in the first days after rapid AED withdrawal. Non-adherent patients were identified by not presenting the expected fall in PLs. It was found that low PLs were equally frequent in adherent and non-adherent patients and were often caused by PK interaction with enzyme-inducing drugs or had other reasons. In other words, non-adherent patients were as likely to have unsuspicious, average PLs as they had low PLs.

However, AED levels become an important tool to discover non-adherence when the individual therapeutic level is known. If an unexpected seizure needs to be clarified, a blood sample should be taken as soon after the seizure as possible to obtain a quasi-ictal PL[5]. A substantial decrease in spite of unchanged dose and preparation is highly suspicious of incomplete intake (although other possible factors like new enzyme-inducing co-medication, acute febrile illness or others as described above still need to be ruled out).

Pharmacoresistance

It is important that pharmacoresistance is clearly identified so other options such as epilepsy surgery can timely be considered. There is a broad consensus that surgery should be discussed when two correct and conclusive trials with appropriate drugs have failed[4]. A correct trial implies that the patient still had seizures with the highest tolerated dose. To identify it, PL measurements are indispensable. The "highest tolerated dose" implies a PL at the upper end of the middle reference range or above. Since tolerability of AEDs is highly variable, it can be necessary to increase dose and PL until the first signs and symptoms of toxicity occur. Then, the previous dose clearly is the highest tolerated dose. Side effects at a lower PL than the highest tolerated are usually not dose-related but idiosyncratic effects indicating that the drug is unsuitable for the patient. In this case, the trial does not count towards resistance but is considered "undetermined"[4].

Table 2: When should plasma levels be determined?

AT TREATMENT ONSET WHEN THE FIRST TARGET DOSE IS REACHED AND A STEADY STATE PL CAN BE EXPECTED.
This measurement provides information on the patient's individual level-to-dose ratio, which allows to calculate the development of PL after changes of dose.

WHEN A PATIENT HAS BEEN SEIZURE FREE LONG ENOUGH TO ASSUME THAT THE FULL THERAPEUTIC EFFECT HAS PROBABLY BEEN REACHED.
This measurement provides a tentative individual therapeutic PL.

WHEN A PATIENT HAS A SEIZURE AFTER HE WAS ASSUMED TO BE SEIZURE FREE.
This measurement needs to be compared with the previous tentative therapeutic PL. If the present PL is lower, the reason must be found and corrected (e.g. non-adherence? enzyme-inducing new co-medication? preparation shift?). If the PL is as expected, the tentative therapeutic PL is disproved and the PL after a dose increment becomes the new assumed therapeutic level.

AT CHANGE OF PREPARATION
Generic preparations have in cohort studies been shown to be bioequivalent with the brand. However, the generic may *individually* be non-equivalent. In addition, preparation shifts in practice often take place between various generic preparations whose inter-bioequivalence usually has not been tested. Preparation shifts therefore may individually result in PL increase with possible toxicity, or PL decrease with possible breakthrough seizures and even a risk of status epilepticus [2].

WHEN A PATIENT COMPLAINS SYMPTOMS SUSPICIOUS OF A DOSE-DEPENDENT SIDE EFFECT.
Toxicity is proved if the PL is above the pre-established individual therapeutic level where there were no such side effects

WHEN A NEW COMEDICATION WITH POTENTIAL PK INTERACTION IS ADDED
In consequence, dose adjustment may be required

DURING PREGNANCY, ESPECIALLY WITH LAMOTRIGINE AND OXCARBAZEPINE
In consequence, dose adjustment may be required

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Conclusions

Therapeutic drug monitoring (TDM) is an important tool for the management of epilepsy but the plasma levels need to be carefully interpreted to reach correct conclusions. Basic principles for its application are given in table 1, and in table 2, typical indications for TDM are listed. The reference ranges indicated by many AED laboratories are not normative but only orienting. Their designation as "therapeutic levels" is misleading and potentially dangerous. Because of the high interindividual variability of seizure propensity, therapeutic levels and ranges can only refer to individual cases, and an individual therapeutic level should always be established as a reference for all questions that might arise.

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