



Measure for Measure: Measuring the Usefulness of Measuring Antiseizure Medication Levels

Therapeutic Drug Monitoring of Newer Antiepileptic Drugs: A Randomized Trial for Dosage Adjustment

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Objective: Therapeutic drug monitoring (TDM) of antiepileptic drugs (AEDs) is widely established for older generation AEDs, whereas there is limited evidence about newer AEDs. Our aim is to assess the benefit of TDM of newer generation AEDs in epilepsy. **Methods:** We performed a randomized, controlled trial comparing systematic with rescue TDM of lamotrigine, levetiracetam, oxcarbazepine, topiramate, brivaracetam, zonisamide, or pregabalin. Participants were adults with epilepsy, in whom treatment with newer generation AEDs was initiated or needed adjustment. In the systematic TDM arm, AED plasma levels were available at each appointment, whereas in the rescue TDM arm, levels were known only if a study end point was reached (inefficacy or adverse events). The primary outcome was the proportion of participants who followed 1 year without reaching one of the predefined end points. **Results:** A total of 151 participants were enrolled; global retention in the study was similar in both arms (56% overall, 58% in the systematic, and 53% in the rescue TDM arm, $P = .6$, Cox regression). There was no difference in terms of outcome regarding treatment efficacy or tolerability. Partial adherence of clinicians to TDM (adjusting or not AED dosage based on blood levels) did not explain this lack of benefit. **Interpretation:** This study provides class A evidence that systematic drug-level monitoring of newer generation AEDs does not bring tangible benefits in the management of patients with epilepsy. Poor correlation between clinical effects and drug levels likely accounts for this finding. However, TDM is useful in several situations, such as pregnancy, as well as when there are compliance issues.

Commentary

Routine use of plasma-level monitoring of newer antiseizure medications (ASMs), according to the report by Aícua-Rapún et al,¹ provided no advantage in terms of seizure control or avoidance of toxicity among a group of 151 patients. Patients were randomly assigned to a cohort who had levels measured at every clinic visit or to a cohort who had levels measured only as a “rescue” measure, that is, if seizure control worsened or if drug toxicities were suspected. There was no difference in outcomes of seizure control or toxicity. This conclusion may be surprising, but it replicated the results of a study published in 2000 of patients with new-onset epilepsy, which also found no measurable advantage to routine monitoring of levels.²

Is it ever useful to measure plasma levels of ASMs, or is it an expensive and potentially misleading practice? Overuse of plasma levels has been criticized for years.³ However, most neurologists still find levels useful in certain circumstances, and there has been an extensive discussion of when they should be measured.^{4,5} A common circumstance is pregnancy, when levels of many ASMs are known to fall substantially. However, even this has been questioned. In a British study, pregnant

women with a plasma level decrease over 26% from a baseline value were randomized to monthly drug-level monitoring or to dosing based on clinical judgment.⁶ Outcomes of seizure number and time to first seizure after randomization did not differ.

What are we to make of these results? Firstly, there is no reason to think that there is something magical about most of the newer ASMs compared to most of the old ones that exempts the prescriber from measuring levels.⁷ It is also useful to reflect on how we arrived at the current standard of practice. Soon after a convenient method of measuring ASM serum levels came into general use,⁸ it became apparent that the relationship between prescribed dose and serum level was highly variable. Variations occur because of genetic and environmental differences in absorption, metabolism, and excretion, by diurnal fluctuations, by drug interactions, and by adherence. Thus from the beginning of the era of plasma-level monitoring, caution was advised. In 1969, Pippenger et al⁸ stated that “Interpretation of the significance of a given level in the blood must be based on the clinical evaluation of the patient in conjunction with the laboratory findings.” There is a story, perhaps apocryphal, that the time-honored therapeutic range of phenytoin, 10 to 20 $\mu\text{g/mL}$, was decided by 2 neurologists



speculating over beers. Nevertheless, it seemed to be about right, and was eventually supported by systematic studies.

The good advice to be cautious in interpretation of levels is often forgotten. This can lead to dangerous reductions in dose because of a “toxic” level which in fact may have been perfectly well-tolerated and necessary for seizure control. Less dangerous but still expensive and generative of side effects is the practice of raising doses because of a “subtherapeutic” level in persons who are seizure-free.^{4,5}

How do we select patients who need levels measured? There are 3 categories of patients: those with seizures, those with toxicity, and those who are just fine. Most patients in all 3 categories do not need levels: the course of action is clear. For those with seizures, as a check for adherence, a single level is worthless unless compared with previous levels in the same patient.⁹ For those with toxicity, identification of the culprit drug in polytherapy is also unreliable. The drug with the low serum level may be responsible. Patients who are just fine would seem to constitute a group that never needs a plasma level. But there is an exception: patients with new-onset epilepsy with infrequent seizures. In such patients, one cannot “titrate to effect” because the infrequent seizure has not yet recurred. It is then necessary to titrate to a predetermined dose or to a predetermined plasma level. A dose target may be satisfactory if there is a well-established relationship between dose and efficacy, or if serum levels are known not to reflect degree of brain binding (levetiracetam). But for most drugs, aiming for a target serum level makes more sense. I am uncomfortable with a lamotrigine level of 3 µg/mL in a patient with new-onset epilepsy, regardless of the prescribed dose. If non-adherence is ruled out, the dose should be raised. Another possible use for a level is to set a “baseline” when the patient is doing well for future reference. This is the concept of setting an “individual reference range” rather than a population reference range.^{3,4}

It may be argued that regulatory agencies do not consider serum levels in deciding efficacy of new ASMs. That is generally true, but it has more to do with the practicalities of running a clinical trial than with any scientific reason. Drugs which do not show a good step-wise relationship between dose and efficacy are unlikely to be approved. It would make more sense to assess the serum (or brain/cerebrospinal fluid) level-efficacy relationship. The National Institute of Neurological Disorders and Stroke tried to bridge this gap by sponsoring a “concentration-response trial” of a new drug in the early 1990s, but by sheer bad luck, the drug they chose was felbamate, so the trial was never completed nor published.


What about pregnancy? At our institution, we have an epilepsy/pregnancy clinic which features frequent follow ups and frequent serum levels of most drugs. Is that a waste of time and money? That conclusion seems unlikely. The British study⁶ did not completely prove an absence of difference (in my opinion noninferiority was not proved); more data are needed. Besides,

prevention of even one infrequent serious event—a tonic-clonic seizure during pregnancy—may have a cost-benefit worth which is not reflected in the group data. We probably could calculate a “number needed to measure” to prevent “one seizure” and attach costs to each, but that would not be very useful. Rare but catastrophic events are still worth preventing. Airplanes rarely run out of fuel, so time spent checking the fuel gauge may not be time-efficient for pilots, but no one would advise skipping it.

In summary, Aícua-Rapún et al have reported a lack of benefit of routine plasma-level monitoring of ASMs, but the key word is “routine.” There are still valid indications for checking levels. For patients with new-onset epilepsy beginning therapy, and most likely for pregnant women, correction of a low or dropping serum level may prevent a seizure. And even an occasional seizure is dangerous.

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