



Don't Get Fooled by Misleading Serum Levels of Antiepileptic Medications

Manipulating AED levels is challenging in and of itself. Unfortunately, confusing terminology can further complicate the process. Here's what to watch out for.

Since 1990, the Food and Drug Administration approved the use of eight new antiepileptic drugs (AEDs), as well as new formulations of older medications. Other AEDs are now being studied and may soon be available. The greater number of treatment options promises a better quality of life for those with seizures. However, an expanded pool of treatment options also poses a greater challenge to the physician. Which medication is most effective for certain seizure types? How are seizure medicines best combined? What is the optimal dosing schedule? What do the serum levels mean? How often should I check blood levels?

These are just a few questions every neurologist faces. We have touched on some of these issues in past installments of this column. This month, we will focus on serum levels, and how they may help to optimize the treatment of epilepsy.

The "Therapeutic Range"

What does "therapeutic range" really mean? The term itself is misleading, because it suggests that "good levels" equals "good seizure control," levels that are "low" mean poor seizure control, and levels that are "high" indicate "toxicity" or the development of side effects. Of course, all this is simply untrue. Some people require "high" levels in order to maintain complete seizure control, and some will be well-controlled with "low" serum levels of an AED. Similarly, some people will experience side effects at "low" levels of AEDs, while others may be free of adverse events even at very "high" serum levels. The best measure of effectiveness can be answered

by two simple questions, posed at each office visit: "Are you having seizures?" and "Are you having side effects?"

Most therapeutic ranges are statistically derived from populations of people taking the medication (see Table 1). Instead of "therapeutic range," a better term might be "reference range." A serum value below the reference range would indicate that a person is more likely to continue to have seizures and less likely to experience side effects. Values that are above the reference range indicate that side effects are more likely to happen. In other words, the "reference range" is really a guide to therapy. Levels, when checked, should be combined with good clinical decision-making in order to optimize the quality of life.

Another issue that must be considered is when the serum level was drawn in relationship to the last dose of medication.¹ Serum levels of all medications fluctuate during the course of a day. A peak level occurs after a dose is taken, falls as the medication is metabolized, and reaches a trough just before the next dose is administered. Knowing when the level was drawn in relationship to the last dose will help to determine whether the level represents a peak or trough, and may help the clinician to optimize the dose of medication.

When are Levels Helpful?

When a medication has complex pharmacokinetics (regarding absorption, metabolism or excretion) it can be more difficult to anticipate changes in serum levels as they relate to changes in the dose of medication.² Phenytoin is the best example of this. It has zero-order kinetics. At lower doses, there is a linear relationship between

the dose of phenytoin and its serum level. However, at higher doses, the metabolism of phenytoin becomes saturable. When this occurs, even small increases in the dose of medication will result in a large increase in the serum levels. Since there is no way of knowing when an individual will reach this point, monitoring levels may be needed in order to more carefully adjust the dose of medication.

Documentation of a serum level may be helpful when a person's seizures are well-controlled. The measurement then serves as a "baseline" to which future values can be compared, should seizure control worsen. Non-compliance is a good example of this. A person may become complacent when his seizures are well-controlled. He may begin "missing" doses of medication, resulting in a drop in serum levels, and a return of seizures. The "baseline" level would serve as a target to which the physician could aim.

The metabolism of many AEDs changes during pregnancy.³ The effect is variable, resulting in either a higher or lower-than-expected serum level. As the pregnancy progresses, the levels will continue to change. Therefore, careful monitoring of serum AED levels throughout the pregnancy is required. As the levels change, the dose of medication may need to be increased (or decreased) in order to maintain the baseline level, and therefore good seizure control.

Metabolism and excretion of AEDs may change for other reasons. Medical illnesses which result in either hepatic or renal impairment may mean a reduced metabolism and elimination of drug. As we get older, the metabolism and excretion

Table 1. The “Reference Range” for Commonly Prescribed AEDs

AED	“Usual” Daily Dose	Reference Range
carbamazepine	400-1800+ mg	4-12 ug/ml
ethosuximide	500-1500+ mg	40-100 ug/ml
felbamate	1200-4800+ mg	30-100 ug/ml
gabapentin	900-3600+ mg	4-20 ug/ml
lamotrigine	200-800+ mg	4-20 ug/ml
levetiracetam	1000-4000+ mg	5-40 ug/ml
oxcarbazepine	600-2700+ mg	10-40 ug/ml
phenytoin	200-400+ mg	10-20 ug/ml
phenobarbital	90-180+ mg	20-40 ug/ml
tiagabine	12-64+ mg	100-300 ng/ml
topiramate	100-600+ mg	10-20 ug/ml
valproate	750-2500+ mg	50-100 ug/ml
zonisamide	100-600+ mg	10-40 ug/ml

of medications slows. In both cases, the result is a higher serum level at relatively low doses of AED. Clinically, this may translate into side effects, necessitating a decrease in the dose (or dosing schedule). The opposite is generally true in children, who have a more rapid metabolism and excretion of medication. Higher doses may be needed to produce serum levels which translate into good seizure control.

Polypharmacy may produce complex drug-to-drug interactions. Some AEDs are hepatic enzyme inducers (*e.g.*, carbamazepine, oxcarbazepine, phenytoin, phenobarbital). When these are used in conjunction with another medicine that is broken down by the same metabolic pathway, the metabolism of the second drug will be sped up, resulting in lower serum levels. On the opposite end of the spectrum are the hepatic enzyme inhibitors (*e.g.*, valproate). Co-administering this agent may result in an increased level of another medication. If the patient is on a combination regimen and another AED is added, predicting the serum level becomes even harder. Obtaining serum levels may help define the complex interactions between drugs when using polypharmacy.

Pitfalls to AED Levels

Doctors and patients are prone to falling into a number of pitfalls. As we all know, there are limits to medical testing. It is rare that a single medical test will make the diagnosis. Instead, medical tests must be combined with solid clinical judgment in order to determine the diagnosis and best therapeutic course of action. When treating seizures, the goal is seizure freedom without side effects: monitoring serum levels may be helpful, but does not replace clinical judgment in optimizing the quality of life of a person with epilepsy.

“High” serum levels do not necessarily equate with “toxicity.” This problem occurs far too often in clinical practice. Many physicians have been awakened by well-meaning laboratories who call to inform the doctor about “critically high” or “toxic” levels. The determination as to whether side effects are occurring must be made at the bedside. A detailed questionnaire and physical exam will identify patients who are experiencing adverse events. This must be done at each office visit, as interval changes in medication doses must be carefully monitored. Every person is different: some will develop side effects at “low” levels, while others will be free of problems even at “high” levels. Adjusting a medication simply on the basis of “high” levels may not be in the patient’s best interest: if a person’s seizures were well-controlled, lowering the dose may compromise this.

Similarly, “low” levels do not equate with poor seizure control. For the same reasons mentioned above, some people will have complete seizure control at low doses, while others will require high doses of medication. A careful history is needed in order to establish that the patient has good seizure control. If a person with seizures had good seizure control at a “low” level, responding to a “low” level by increasing the dose might

result in toxicity, while offering no improvement in seizure control.

Lastly, “therapeutic” levels do not equate with good seizure control: obtaining a therapeutic AED level does not guarantee that a person will stop having seizures. Here again, the treatment must be adjusted according to the individual. We have already seen that some individuals need a high level in order to meet the goals of therapy. If a physician were to stay within the therapeutic range, he or she may never increase the medication to the dose which is optimal for that individual. In other words, the physician would be under-dosing the patient. The result is poor seizure control and a lesser quality of life.

Keep it in Context

The goal of epilepsy treatment is simple: seizure freedom without side effects. An individual’s response to medication, however, may be quite difficult to predict. Some will have good seizure control at “low” levels of medication, while others will experience side effects at the same “low” doses. Similarly, there are people who will need “high” serum levels of AEDs to be seizure-free. They may experience no problems, even at these high doses.

Serum levels may be helpful in many clinical situations: complex pharmacokinetics, changes in metabolism or excretion of drugs, and during polypharmacy, where unpredictable drug-to-drug interactions may occur. Serum levels should be interpreted in the context of the clinical situation. It is only by combining these tests with solid clinical judgment that the best quality of life can be attained. **PN**

1. Theodore WH. Rational use of antiepileptic drug levels. *Pharmacol Ther* 1992;54:297-305.
2. Leppik IE. Laboratory Tests. In, *Epilepsy: A Comprehensive Textbook*, edited by J. Engel and T.A. Pedley. Lippincott-Raven Publisher, Philadelphia 1997. Pp 811-817.
3. Pennell PB. Pregnancy in women who have epilepsy. *Neurol Clin* 2004;22(4):799-820.

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