

Monitoring antiepileptic drug therapy with serum level measurements

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We treat patients, not levels

The goal of therapy with antiepileptic drugs (AEDs) is to prevent all seizures, using drugs that produce minimal side effects. Success in achieving this goal must be assessed clinically. Routine ordering of tests to measure AED levels is misguided, given that the tests are costly and often unnecessary.¹

Therapeutic drug level monitoring was introduced because of a belief that drug levels in the blood were a more reliable indicator of efficacy than drug dose alone. Although this relationship applied to phenytoin, the main drug in use three decades ago, it does not apply to many AEDs.

The concept of a "therapeutic range" is a statistical concept, applying to populations rather than individuals. There are many patients whose condition is perfectly well controlled with so-called subtherapeutic doses, while other patients may require more than the recommended therapeutic dose. For most patients, management need not involve serum drug measurements. They are certainly unnecessary for the so-called second generation AEDs or for benzodiazepines, which are selectively taken up by the brain and for which serum level measurements are not meaningful for management.²

Sodium valproate (SVP) is widely used. The relationship between SVP serum levels and efficacy has not been confirmed, and serum testing is often inappropriate, as reported in this issue of the *Journal* (page 582).³ On conventional doses of SVP (which should be kept under 1000 mg per day in women of childbearing age), most compliant patients achieve a serum level within the so-called therapeutic range, which is wide (350–700 µmol/L). Previous studies have shown that results of SVP assays do not influence the doses used in management.⁴ If the results are not acted on, the tests are a waste of time and money. On the other hand, patients can be destabilised if the results of SVP assays directly influence doctors to alter doses regardless of clinical indications.^{5–7}

For the AEDs topiramate, vigabatrin, oxcarbazepine, gabapentin and levetiracetam, insufficient data are available to justify serum level monitoring. In fact, for vigabatrin, which acts by permanent inhibition of an enzyme related to neurotransmitters, measuring levels is totally unnecessary.⁴

Lamotrigine may represent a special category. The metabolism of this drug is induced by sex hormones in the oral contraceptive pill and is also altered during pregnancy. In these circumstances, the drug is rapidly eliminated. It may be helpful to measure lamotrigine concentrations in each trimester to keep them at pre-pregnancy levels by adjusting the dose. At delivery, the dose must be reduced.

There is no accepted therapeutic range for lamotrigine, and the concept of individual ranges has been proposed. Once a level is established that is associated with good control of the patient's seizures, this level may be a target to be aimed at when changes are made to AED doses and co-medications in that particular patient. However, routine measurements are not recommended.⁸

Thus, with the exception of phenytoin (and possibly lamotrigine), none of the AEDs are suitable candidates for therapeutic drug monitoring assays in routine practice, as such tests put a high cost burden on the health service without significant patient benefit.

The International League Against Epilepsy guidelines state that AED serum concentrations must not be measured indiscriminately and that adjusting doses merely to achieve cosmetic correction of levels is inadvisable. However, compliance problems can be an indication for performing an assay.⁹

In conclusion, we treat *patients*, not *levels*. The rationale for performing drug assays should be based on clear indications for why they are to be ordered. Clinical symptoms, inadequate response and possible toxicity may be valid indications, but the most important one appears to be suspicion of non-compliance.

Competing interests

I am the Director of the Australian Pregnancy Register of Antiepileptic Drugs, a research initiative supported by the Epilepsy Society of Australia, a National Health and Medical Research Council linkage grant, and all the pharmaceutical companies involved in the anticonvulsant field. These companies include GlaxoSmithKline, Janssen-Cilag, Mayne, Novartis, Pfizer, Sanofi and UCB. I have received honoraria for speaking at or attending international meetings to present data relating to the Register and for attending educational meetings in Australia.

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