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## FPIN's Clinical Inquiries

### Antiepileptic Drug Level Monitoring

WAIL MALATY, MD, *Mountain Area Health Education Center Rural Track Family Practice Residency, Hendersonville, North Carolina*

SUE STIGLEMAN, MLS, *Mountain Area Health Education Center, Asheville, North Carolina*

Clinical Commentary by PETER C. SMITH, MD, *University of Colorado Denver School of Medicine, Denver, Colorado*

#### Clinical Question

Is monitoring antiepileptic drug levels necessary?

#### Evidence-Based Answer

Routine monitoring of antiepileptic drug levels does not alter seizure or side effect rates. (Strength of Recommendation [SOR]: B, based on a single randomized controlled trial [RCT] with less than 80 percent follow-up). Antiepileptic drug level monitoring may be clinically useful in special populations, including patients with suspected drug toxicity or noncompliance, pregnant patients, and patients with renal failure. Monitoring dosage increases of drugs with nonlinear kinetics, such as phenytoin (Dilantin), may be useful. (SOR: C, based on expert opinion). Therapeutic drug level monitoring of newer antiepileptic drugs has not been shown to be clinically useful. (SOR: C, based on expert opinion).

#### Evidence Summary

Antiepileptic drug level monitoring has been routinely used since the advent of reliable assays of phenytoin levels in the 1960s.<sup>1,2</sup> At times, drug level monitoring is unnecessary and possibly harmful (e.g., indiscriminate antiepileptic drug level monitoring in a stable patient may create the potentially dangerous situation of treating the level and not the patient).<sup>3</sup> A study of antiepileptic drug level determinations at a tertiary care center revealed that only 27 percent were appropriately indicated, and of those, one half were sampled incorrectly.<sup>4</sup>

One RCT assessed the impact of antiepileptic drug level monitoring in patients with new-onset epilepsy.<sup>5</sup> The study enrolled 180 patients with partial or idiopathic generalized epilepsy treated with carbamazepine (Tegretol), valproate (Depakote), phenytoin, phenobarbital, or primidone (Mysoline). Using an open-label, parallel group design, patients were randomized to two groups (a monitored group or a control group). In the monitored group, drug dosage was adjusted to achieve a therapeutic level. In the control group, drug dosage was adjusted on clinical grounds. Sixty-four percent of the patients completed the two-year study. There was no significant difference between the monitored and control groups in the proportion of patients who achieved a 12-month seizure-free remission (60 versus 61 percent, respectively; hazard ratio (HR) =

0.96; 95% confidence interval, 0.50 to 1.63). The incidence of side effects was similar in the monitored and control groups (48 versus 47 percent, respectively). A recent Cochrane review singles out this study as the only one meeting its inclusion criteria, and concurs with its conclusions.<sup>6</sup>

As for the newer antiepileptic drugs, including gabapentin (Neurontin), lamotrigine (Lamictal), oxcarbazepine (Trileptal), and topiramate (Topamax), there are no well-established therapeutic or toxic drug levels.<sup>7</sup> Thus, routine monitoring of levels of these drugs is generally not clinically useful. There are several clinical situations in which antiepileptic drug level monitoring may be useful. These are summarized in *Table 1*.<sup>1,8,9</sup>

**Table 1. Clinical Situations in Which Antiepileptic Drug Level Monitoring May Be Useful**

<i>Clinical situation</i>	<i>Rationale</i>	<i>Strength of recommendation</i>	<i>References</i>
Suspected noncompliance	Determine probable cause of seizures.	C	1, 8
Suspected drug toxicity	Decrease drug dosage to achieve nontoxic level.	C	1, 8
Increase phenytoin (Dilantin) dosage	Nonlinear kinetics may result in toxic level.	C	1, 9
Renal failure	Decreased drug protein binding may render "therapeutic" level toxic.	C	8, 9
Pregnancy	Decreased drug protein binding may render "therapeutic" level toxic.	C	8, 9

*A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series.*  
*Information from references 1, 8, and 9.*

## Recommendations from Others

The Commission on Antiepileptic Drugs of the International League Against Epilepsy does not support indiscriminate use of antiepileptic drug level determinations.<sup>3</sup> It also cautions that using drug levels to adjust dosage so that the numbers fall within the therapeutic range is a waste of time and money, and could possibly be dangerous if drug therapy is effective and well tolerated. It recommends tailored determinations if patients show signs of toxicity, if noncompliance is suspected, or if patients have persistent seizures despite large dosages of drug. Also, monitoring drug level is reasonable when drugs with zero order (nonlinear) kinetics (e.g., phenytoin) are not effective and the dosage is increased, or in patients with an abnormal ratio of total to free drug levels (e.g., pregnant women).

The National Collaborating Centre for Primary Care states that regular drug level monitoring in adults is not routinely recommended and should only be done if clinically indicated.<sup>10</sup>

## Clinical Commentary

There are a few important caveats to this review that reflect the complexity of clinical practice and that concern several issues not covered in these trials. First, the data presented here indicate active clinical

assessment and surveillance for antiepileptic side effects. Physicians treating patients with seizure disorders should be familiar with common agent-specific side effects, including gastrointestinal side effects, vertigo, and ataxia with carbamazepine; nystagmus, ataxia, mental status changes with phenytoin; and tremor, ataxia, lethargy, facial edema, anorexia, weight gain, and platelet dysfunction with valproate. Physicians should also be aware of rare but serious side effects, such as blood dyscrasias, Stevens-Johnson syndrome, respiratory depression, hepatic failure, and pancreatitis. Second, many of these drugs, especially phenytoin, have multiple drug interactions that may cause an effect of "increase in dosage." In these cases, it seems appropriate to check levels when starting therapy, especially with long-term medications. Third, drug level monitoring is not the only monitoring required with these drugs. For example, carbamazepine and phenytoin require a complete blood count at initiation and periodic hepatic and renal function monitoring; and valproate requires periodic monitoring of liver function tests, especially in the first six months. Fourth, in my teaching practice we see many patients with epilepsy and developmental delays who are nonverbal or who may exhibit symptoms similar to antiepileptic side effects at baseline (e.g., ataxia, nystagmus, dysarthria, tremor). Accordingly, assessing these patients for side effects is challenging, and I would include them in the list of special populations that require regular monitoring mentioned in this review. Finally, knowing the proper timing of sample collection is essential to avoiding errors. Carbamazepine, valproate, and oral phenytoin should be tested after steady state has been reached, just before the next dose is given, and at a consistent time of day.

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Address correspondence by e-mail to Wail Malaty, MD, [wail.malaty@pardeehospital.org](mailto:wail.malaty@pardeehospital.org) Reprints are not available from the authors.

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