MAKING SENSE OF LAMOTRIGINE SERUM LEVELS

Correlating Lamotrigine Serum Concentrations with Tolerability in Patients with Epilepsy

Hirsch LJ, Weintraub D, Du Y, Buchsbaum R, Spencer HT, Hager M, Straka T, Bazil CW, Adams DJ, Resor SR Jr, Morrell MJ
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OBJECTIVE: To correlate lamotrigine (LTG) serum concentrations (levels) with tolerability in patients with epilepsy.
METHODS: The charts of 811 outpatients with epilepsy who had received LTG and were seen at the Columbia Comprehensive Epilepsy Center after January 1, 2000, were reviewed. Data gathered included levels, dosage, duration of use, concomitant antiepileptic drugs (AEDs), clinical toxicity, specific side effects, and efficacy. Rates of toxicity, specific side effects, and efficacy were calculated and correlated with serum levels.
RESULTS: In total, 3,731 LTG levels were recorded. A regimen was categorized as toxic if the patient experienced side effects that led to a dosage change or discontinuation of LTG. Of 3,919 AED regimens, 9.4% were toxic, and 30.7% of patients had at least one toxic regimen. Toxicity increased with increasing LTG levels ($P < 0.0001$): With levels less than 5.0 μg/mL, 7% of patients were toxic; with levels of 5 to 10 μg/mL, 14%; with 10 to 15 μg/mL, 24%; with 15 to 20 μg/mL, 34%; and with more than 20 μg/mL, 59%. The correlation between levels and tolerability was independent of concurrent medication. Increasing efficacy, as measured by seizure freedom for a 6-month period, occurred up to levels of more than 20 μg/mL.
CONCLUSIONS: A correlation exists between LTG serum level and tolerability, independent of the use of other AEDs. Adverse effects requiring a dose change are uncommon with the most frequently encountered LTG concentrations (<10 μg/mL) and occur in only 7.4% of patients at levels obtained during the majority of clinical trials (<5 μg/mL). An initial target range of 1.5 to 10 μg/mL is suggested, although higher levels, up to more than 20 μg/mL, are often tolerated and can lead to additional efficacy in refractory patients.

COMMENTARY

Serum concentrations can be measured for all the new antiepileptic drugs (AEDs), but generally limited understanding exists of how to interpret and use this information. It also is argued that serum levels may not be relevant and that treatment should be based purely on clinical response and adverse effects. In the case of lamotrigine (LTG), this position was supported by a failure to demonstrate a useful concentration-effect or concentration-toxicity relation in one early study (1).

Roughly 50% of patients become seizure free with the first AED and usually do so at low doses (2). However, in approximately 35% of patients seizures prove refractory (3) and may require dose escalation. Even when the dose escalation is guided by seizure control and adverse effects, once a dose is reached that is considered too high, according to prescribing information guidelines, most physicians will be inhibited from further escalation. An AED serum level may be a helpful guide in such situations to determine how much leeway there is for further dose increases.

Hirsch et al. have identified a clear relation between LTG serum concentrations and tolerability in patients with epilepsy ($P < 0.0001$). Patients with drug levels exceeding 20 μg/mL appeared to have a high likelihood of developing symptoms of toxicity, while toxicity occurred infrequently at levels of 10 μg/mL and less. In the discussion, the authors present a thoughtful assessment of situations in which an LTG serum level would be helpful. A drug serum level is important in identifying noncompliance; in addition, a baseline level is quite helpful as an internal reference for the patient. Serum levels are particularly important for a medication, such as LTG, whose clearance is increased by oral contraceptives, by pregnancy, and by enzyme-inducing drugs and decreased by valproate as well as other agents.

Whereas a serum drug level should not be the primary guide for treatment, it can be very helpful in assisting the evaluation of refractory seizures, particularly when it is not clear whether the drug has failed or has not been sufficiently escalated. In addition, the authors argue that serum levels can be useful to guide dosing in patients with infrequent seizures for whom it would be appropriate to increase the dose until at least an average serum level is obtained.

by Bassel W. Abou-Khalil, M.D.

References

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