

WHEN THINKING OF LAMOTRIGINE AND VALPROIC ACID, THINK “PHARMACOKINETICALLY”!

Evaluation of VPA Dose and Concentration Effects on Lamotrigine Pharmacokinetics: Implications for Conversion to Lamotrigine Monotherapy

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OBJECTIVE: Lamotrigine (LTG) is approved for monotherapy after discontinuation from enzyme-inducing antiepileptic drugs (AEDs). LTG also is frequently used in combination with sodium valproate (VPA), and discontinuation to monotherapy in this setting also is frequently desirable. Given the known pharmacokinetic interaction between these two drugs, clinically relevant questions that should be answered include (a) at what dose and/or concentration of VPA does this interaction begin, and (b) at what dose of VPA does maximal inhibition occur?

METHODS: LTG pharmacokinetics was evaluated by using single-dose LTG (25 mg) given before and after low-dose VPA comedication (125, 250, 375, and 500 mg/day VPA) in healthy subjects. Serial blood samples were obtained over 120 h after dose to calculate LTG kinetic parameters including area under the concentration–time curve, apparent oral clearance, elimination half-life, and percentage inhibition of LTG clearance at each dosage level of VPA. Pharmacodynamic modeling was used to calculate median effective dose (EC_{50}) values for this interaction.

RESULTS: LTG pharmacokinetic parameters were evaluated in adult healthy female and male volunteers. Mean trough VPA concentrations at doses of 125, 250, 375, and 500 mg/day were 6.5, 13.9, 16.1, and 31.9 $\mu\text{g/ml}$, respectively. Maximal theoretical inhibition of LTG oral clearance by VPA is approximately 65%, with an EC_{50} concentration value of approximately 5.6 $\mu\text{g/ml}$ of VPA. Mean inhibition of LTG oral clearance during concomitant treatment with VPA, 125, 250, 375, and 500 mg/day, was 30.8, 51.5, 52.8, and 50.3%, respectively.

CONCLUSIONS: These data suggest that VPA inhibition of LTG clearance begins at very low VPA doses and concentrations. Maximal inhibition can be expected at VPA doses of approximately 500 mg/day, with the magnitude of inhibition diminishing at doses below this. These data provide useful information to develop a dosing algorithm to facilitate conversion to LTG monotherapy.

COMMENTARY

Now and then, we encounter studies in the antiepileptic drug (AED) literature that have a very significant impact on the daily practice of neurologists. The article by Gidal et al. presents one such study. Despite the sophisticated pharmacokinetic and statistical analyses, which undoubtedly are foreign to most clinicians, the data are clearly depicted in a series of graphs that convey the take-home message: valproic acid (VPA) inhibits the clearance of lamotrigine (LTG) by a mean of approximately 30% at a dose of 125 mg/day and by a mean of 50% at doses of 250 mg and higher. These data complement findings from a previous study that demonstrated a maximal inhibition of LTG clearance by VPA at doses of 500 mg/day, but in which lower doses were not tested (1). The first practical implication of these data applies to the conversion from a VPA plus LTG therapy to LTG monotherapy: the dose of LTG may be kept unchanged until the dose of VPA is lowered to 125 mg/day, at which point, the dose of LTG must be increased by 30% and, finally, doubled on the day VPA is discontinued.

Yet these data have practical implications beyond the conversion from VPA plus LTG to LTG monotherapy. First, low-dose (250 mg/day) VPA potentially can be considered for use exclusively as an inhibitor of LTG clearance—particularly in patients for whom cost of medication is a concern, as it can cut LTG cost by 50%. Furthermore, at such a low dose, the risk of adverse events related to VPA (e.g., weight gain, dysmenorrhea in women of child-bearing age) or to the combination of LTG and VPA (i.e., tremor) is lower than when VPA is used at doses high enough to yield an antiepileptic effect.

Second, the use of low-dose VPA as an inhibitor of LTG clearance may help achieve a successful conversion from a polytherapy regimen of LTG with an enzyme-inducing

AED (such as phenytoin, carbamazepine, phenobarbital, or primidone) to LTG monotherapy. Indeed, in the presence of an enzyme-inducing AED, LTG clearance remains high and its serum concentration low, until 1 to 6 weeks from the time the enzyme-inducing AED is discontinued. The low LTG serum concentrations may fail to yield the anticonvulsant protection necessary to avert seizure occurrence during the tapering of the enzyme-inducing AED dose. The inhibitory effect of VPA on LTG clearance results in an increase of LTG serum concentration. At the time of discontinuation of the enzyme-inducing AED, the dose of VPA can be lowered to 125 mg/day and stopped 1 week later.

Third, the data from this study also can be applied to the conversion of an LTG monotherapy to a polytherapy regimen with VPA. Indeed, these data confirm the fact that the inhibition of LTG clearance by VPA is immediate; accordingly, the dose of LTG can be cut by 50% on the day that VPA is started at doses of 250 mg/day or higher and still ensure that the maintenance of LTG serum concentrations are stable, as shown in a previous study (1). Although the addition of LTG to VPA may increase the risk of rash, unless LTG is introduced at a low dose and tapered up slowly, the addition of VPA, per se, to an LTG regimen does not increase such risk, as the patient has already taken LTG for a long enough period to become desensitized to this effect of the drug (2). Unfortunately, this

misunderstood risk has often limited the use of an LTG plus VPA combination, which potentially can yield a significant improvement in seizure frequency in patients with refractory epilepsy because the AED combination appears to have synergistic therapeutic effects (1,3, 4). Clearly, the article by Gidal et al. is an example of applied pharmacokinetics at its best. The question is, Why did it take 10 years from the time LTG was released in the United States for these essential data to come to the fore? Are clinicians not thinking “pharmacokinetically” enough?

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References

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