Effect of Antiepileptic Drug Comedication on Lamotrigine Clearance

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Objective: To investigate the effect of antiepileptic drug (AED) comedication, including all newer AEDs, on lamotrigine clearance (CL).

Design: We reviewed 570 medical charts of outpatients 12 years and older seen at the Columbia Comprehensive Epilepsy Center who received lamotrigine as monotherapy or adjunctive therapy. We investigated whether a given comedication contributed to the lamotrigine serum concentration. In addition, we examined whether the mean lamotrigine CL during comedication with each AED differed from the lamotrigine CL during monotherapy. Finally, we examined whether individuals had significantly different lamotrigine CLs when taking or not taking a particular comedication.

Results: Comedication with phenytoin, carbamazepine, and valproate sodium were the major AED predictors of lamotrigine serum concentration. Comedication regimens with felbamate, oxcarbazepine, and phenobarbital were small but significant predictors. The mean lamotrigine CL was 43.2 mL/h per kilogram of body weight with lamotrigine monotherapy, significantly higher with comedication with phenytoin (101.3 mL/h per kilogram) and carbamazepine (59.5 mL/h per kilogram) and significantly lower with valproate (16.9 mL/h per kilogram). Patients had significantly higher lamotrigine CL when taking phenytoin, carbamazepine, and phenobarbital than when not taking those comedications and had significantly lower lamotrigine CL when taking valproate. The mean lamotrigine CL was significantly lower than that associated with monotherapy in patients comedicated with valproate plus phenytoin (22.0 mL/h per kilogram) but not in patients comedicated with valproate plus carbamazepine (33.3 mL/h per kilogram). No other AEDs affected lamotrigine CL.

Conclusion: Phenytoin increases lamotrigine CL by approximately 125%, carbamazepine increases lamotrigine CL by approximately 30% to 50%, and valproate decreases lamotrigine CL by approximately 60%. No newer AED, with the possible exception of oxcarbazepine, has a major impact on lamotrigine CL.

Arch Neurol. 2005;62:1432-1436

LAMOTRIGINE IS AN ANTIEPILEPTIC DRUG (AED) that was approved in the United States in 1994. It is indicated as adjunctive therapy for partial seizures in adults and children 2 years and older, conversion to monotherapy in adults with partial seizures receiving treatment with a single enzyme-inducing antiepileptic drug (EIAED) or valproate sodium, and adjunctive treatment of the generalized seizures of Lennox-Gastaut syndrome. Lamotrigine is rapidly absorbed and reaches peak serum concentrations 1.4 to 4.8 hours after administration. The mean half-life of lamotrigine ranges from 25.4 to 32.8 hours in healthy volunteers taking only lamotrigine, 48.3 to 70.3 hours in healthy volunteers comedicated with valproate, and 12.6 to 14.4 hours in patients comedicated with an EIAED. In this study, we examined the effect of AED comedication, including all newer AEDs, on lamotrigine clearance (CL).

METHODS

DESIGN

We reviewed the medical charts of 570 outpatients 12 years and older seen at the Columbia Comprehensive Epilepsy Center between January 1, 2000, and December 31, 2003, who received lamotrigine as monotherapy or adjunctive therapy and who had their weight and lamotrigine serum concentrations (levels) recorded; 2509 lamotrigine levels were available. We excluded levels from patients who were being titrated or who were noncompliant. Levels represented steady-state trough serum concentrations, although time since last dose was not recorded. When a given patient had more than 1 lamotrigine level while taking the same drug combination and lamotrigine dos-
age, levels were averaged, yielding 1345 lamotrigine levels for analysis. The weight-corrected hourly rate of lamotrigine CL was defined by the following formula:

\[
\text{Lamotrigine CL} = \frac{\text{Lamotrigine Weight-Adjusted Daily Dose}}{\text{Steady-State Weight}}
\]

where lamotrigine weight-corrected hourly rate of lamotrigine CL was defined by the following formula:

\[
\text{Lamotrigine CL} = \frac{\text{Lamotrigine Weight-Adjusted Daily Dose}}{\text{Steady-State Weight}}
\]

To investigate each AED comedication effect, 3 analyses were performed. In analysis 1, we examined the correlation of lamotrigine levels with lamotrigine dosage, age, weight, sex, and AED comedication. In analysis 2, we compared the lamotrigine CL during each AED comedication with that associated with monotherapy CL and with other combinations. In analysis 3, we compared the mean lamotrigine CL for an individual when taking vs not taking a particular AED comedication.

**STATISTICAL ANALYSIS**

In analysis 1, multivariate linear regression was used to determine the predictors of lamotrigine serum concentration. Lamotrigine dosage, age, weight, sex, and AED comedication were independent variables, and lamotrigine serum concentration was the dependent variable. In analysis 2, all AED comedication levels were averaged, yielding 1345 lamotrigine levels with lamotrigine dosage, age, weight were significant predictors of lamotrigine level, with lamotrigine levels increasing with age (β = 0.06) and decreasing with weight (β = −0.12). Comedication with felbamate (β = −0.07), oxcarbazepine (β = −0.05), and phenobarbital (β = −0.05) had small but significant inducing effects. The cumulative R² value was 0.38. Other AED comedication and sex were not predictors of lamotrigine serum concentration.

**ANALYSIS 1: PREDICTORS OF LAMOTRIGINE SERUM CONCENTRATION WITH REGRESSION ANALYSIS**

Lamotrigine dosage was the most significant predictor of lamotrigine serum concentration (β = 0.64), followed by comedication with phenytoin (β = −0.30), valproate (β = 0.24), and carbamazepine (β = −0.21). In addition, age and weight were significant predictors of lamotrigine level, with lamotrigine levels increasing with age (β = 0.06) and decreasing with weight (β = −0.12). Comedication with felbamate (β = −0.07), oxcarbazepine (β = −0.05), and phenobarbital (β = −0.05) had small but significant inducing effects. The cumulative R² value was 0.38. Other AED comedication and sex were not predictors of lamotrigine serum concentration.

**ANALYSIS 2: EFFECTS OF COMEDICATION USING ANALYSIS OF VARIANCE**

The variances of the lamotrigine CL with different AED comedications were not equal (P < 0.001, Levene test). Therefore, the lamotrigine CL was transformed using the natural logarithm (ln), after which the variances were not significantly different (P = 0.14, Levene test). In duotherapy, carbamazepine, phenytoin, and valproate had significant effects on lamotrigine CL (P < 0.001 for all). No significant differences were seen with any other AED comedication in duotherapy. The mean lamotrigine CL with phenytoin (101.3 mL/h per kilogram) was significantly higher than that associated with carbamazepine (59.5 mL/h per kilogram), which was significantly higher than with monotherapy (P < 0.001 for both). The mean lamotrigine CL with valproate (16.9 mL/h per kilogram) was significantly lower than

**RESULTS**

The sample comprised 270 male and 300 female patients, whose demographics and lamotrigine data were as follows: mean ± SD (range) age, 43.1 ± 15.9 (12.0-91.8) years; weight, 74.7 ± 18.9 (26.8-163.0) kg; lamotrigine dosage, 434 ± 204 (25-1300) mg/d; and lamotrigine serum concentration, 7.0 ± 3.6 (0.6-21.2) mg/mL.
that associated with monotherapy ($P < .001$). Although the mean lamotrigine CL with phenobarbital (52.2 mL/h per kilogram) or primidone (73.4 mL/h per kilogram) was higher than that associated with monotherapy, there were not enough levels in combination with phenobarbital (n = 20) or primidone (n = 7) to reach significance. The mean lamotrigine CL with valproate plus phenytoin (22.0 mL/h per kilogram) was significantly lower than the mean associated with lamotrigine monotherapy, while the lamotrigine CL with valproate plus carbamazepine (33.3 mL/h per kilogram) was not significantly different than that associated with monotherapy. Results were similar after accounting for age and after excluding 3 patients with hepatic or renal failure. The effect of each AED comedication on the lamotrigine CL is shown in Figure 1.

### ANALYSIS 3: INTRA-INDIVIDUAL PAIRED t TEST

The results were similar in patients when taking vs not taking a given AED comedication (Table 2). Patients who took lamotrigine plus phenytoin and lamotrigine without phenytoin had significantly higher lamotrigine CL when taking phenytoin (94.8 mL/h per kilogram when taking phenytoin vs 40.1 mL/h per kilogram when not taking phenytoin, $P < .001$). Similarly, patients who took lamotrigine plus carbamazepine and lamotrigine without carbamazepine had significantly higher lamotrigine CL when taking carbamazepine, but this effect was smaller than the effect associated with phenytoin (53.3 mL/h per kilogram when taking carbamazepine vs 35.1 mL/h per kilogram when not taking carbamazepine, $P < .001$). Patients who took lamotrigine plus valproate and lamotrigine without valproate had significantly lower lamotrigine CL when taking valproate, demonstrating the inhibiting effect of valproate (20.2 mL/h per kilogram when taking valproate vs 43.0 mL/h per kilogram when not taking valproate, $P < .001$). In addition, the inducing effect of phenobarbital was demonstrated. Patients who took lamotrigine plus phenobarbital and lamotrigine without phenobarbital had significantly higher lamotrigine CL when taking lamotrigine plus phenobarbital (45.2 mL/h per kilogram when taking phenobarbital vs 29.0 mL/h per kilogram when not taking phenobarbital, $P < .001$). There was a trend toward increased lamotrigine CL during comedication with oxcarbazepine, but this effect did not reach significance (51.0 mL/h per kilogram when taking oxcarbazepine vs 37.3 mL/h per kilogram when not taking oxcarbazepine, $P = .09$). No effect was seen in patients taking vs not taking felbamate, although the number of patients with lamotrigine levels when taking vs not taking felbamate was small (n = 4). No effect was seen in patients when taking vs not taking topiramate.

Among those AEDs that affected lamotrigine CL, there was little effect of the dosage or serum concentration of the AED comedication. Neither carbamazepine or phe-
nytoin dosage nor serum concentration correlated with lamotrigine CL. However, valproate dosage (P<.001, r=0.38) and level (P<.001, r=0.63) had an increasingly inhibitory effect on the lamotrigine CL rate (Figure 2). The relationship between valproate dosage and lamotrigine CL was best described by the following logarithmic equation: lamotrigine CL = 40.47 – 0.384 (ln[natural logarithm] valproate dosage).

In this study, we confirmed the results of prior research, defined and quantified the inducing and inhibiting effects of 13 AEDs on lamotrigine CL, and ruled out any major interactions between lamotrigine and the newer AEDs, with the possible exception of oxcarbazepine. Phenytoin has the strongest inducing effect on lamotrigine, more than doubling lamotrigine CL. Carbamazepine has a more modest effect, increasing lamotrigine CL by 30% to 50%. Primidone and phenobarbital also have an inducing effect, although the numbers of patients taking these AEDs were too small to quantify this accurately. No other AED investigated, including all of the newer AEDs, had a major effect on lamotrigine CL, although oxcarbazepine and felbamate demonstrated small statistically significant inducing effects on the lamotrigine serum concentration using regression analysis.

A prior retrospective study demonstrated a 29% inducing effect of oxcarbazepine. In that sample, the inducing effect of oxcarbazepine was approximately half the magnitude of the inducing effect of carbamazepine. A recent placebo-controlled study demonstrated no significant effect of oxcarbazepine, although serum lamotrigine levels were slightly higher with monotherapy. Both of these studies were small; the retrospective study contained only 14 samples from patients taking lamotrigine plus oxcarbazepine, while the placebo-controlled study included only 15 patients in the lamotrigine plus oxcarbazepine cohort. Our study is similarly limited by size, as there were only 19 serum levels among patients taking lamotrigine in combination with oxcarbazepine. Our results suggest that the inducing effect of oxcarbazepine is approximately half that of carbamazepine. This effect may be of clinical significance. With regard to felbamate, a prior study demonstrated a small inhibitory effect of felbamate on lamotrigine, but this effect was not significant statistically or clinically. We found a small but opposite effect. Therefore, it seems that felbamate may have a minor effect on lamotrigine CL, but this effect is not likely to be of clinical significance.

When lamotrigine is taken in combination with valproate plus EIAEDs simultaneously, the composite effect on lamotrigine CL is variable. One study found that the lamotrigine CL when taken with valproate plus phenytoin was not significantly different from that associated with monotherapy, while the lamotrigine CL in combination with valproate plus carbamazepine was significantly lower. Two studies found that the overall effect of valproate plus EIAEDs on lamotrigine levels was not significantly different from that associated with monotherapy. In this study, we find that the effect of the

### Table 2. Effect of Comedication on Lamotrigine Clearance in Individual Patients While Taking vs Not Taking Comedication

<table>
<thead>
<tr>
<th>Comedication</th>
<th>No. of Patients†</th>
<th>Taking Comedication</th>
<th>Not Taking Comedication</th>
<th>Taking Medication–Not Taking Medication Ratio</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Primidone</td>
<td>3</td>
<td>101.3</td>
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<td>2.56</td>
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<td>40.1</td>
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<td>Phenobarbital</td>
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<td>45.2</td>
<td>29.0</td>
<td>1.56</td>
<td>&lt;.001</td>
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<tr>
<td>Carbamazepine</td>
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<td>53.3</td>
<td>35.1</td>
<td>1.52</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
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<td>51.0</td>
<td>37.3</td>
<td>1.37</td>
<td>.09</td>
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<tr>
<td>Topiramate</td>
<td>17</td>
<td>42.8</td>
<td>38.4</td>
<td>1.11</td>
<td>.26</td>
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<tr>
<td>Glibazam</td>
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<td>35.1</td>
<td>33.3</td>
<td>1.05</td>
<td>.39</td>
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<tr>
<td>Vigabatrin</td>
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<td>37.9</td>
<td>37.6</td>
<td>1.01</td>
<td>.88</td>
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<tr>
<td>Levitracetam</td>
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<td>42.7</td>
<td>42.6</td>
<td>1.00</td>
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<td>62.4</td>
<td>0.84</td>
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<td>Zonisamide</td>
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<td>36.9</td>
<td>49.5</td>
<td>0.75</td>
<td>.11</td>
</tr>
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<td>Valproate</td>
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<td>20.2</td>
<td>43.0</td>
<td>0.47</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*When not taking another comedication with an effect on lamotrigine serum concentration as determined by the regression analysis.
†With levels when taking vs not taking comedication.
combination of valproate plus carbamazepine on lamotrigine CL was not significantly different from that associated with monotherapy, while the combination of valproate plus phenytoin still had a significant inhibiting effect (ie, the valproate effect outweighed the phenytoin effect). This is despite the fact that our data suggest that phenytoin is the strongest inducer of lamotrigine metabolism when not combined with valproate.

The finding that increased valproate dosage and serum concentration increasingly inhibit lamotrigine CL confirms the findings of Gidal et al.11,13 and May et al.9 Gidal et al found that valproate inhibition of lamotrigine CL increased with higher valproate dosage until reaching maximal inhibition at a valproate dosage of 500 mg/d. In our sample, low valproate dosages and serum levels have a significant inhibitory effect (Figure 2); however, our data suggest that inhibition continues to increase as valproate dosage is raised, even at valproate dosages higher than 500 mg/d.

One limitation of our data is the lack of detailed information regarding oral contraceptive use. Recently, the effect of oral contraceptives on lamotrigine CL has been demonstrated,16 with lamotrigine serum levels decreasing by greater than 50% in patients comedicated with oral contraceptives. Similarly, we lack detailed information on non-AED comedications and therefore were not able to investigate the possible interaction of these drugs.

The clinical significance of our results is the following: when valproate is combined with lamotrigine, the dosage of lamotrigine will need to be decreased by just over 60% compared with monotherapy to maintain the same serum concentration. When phenytoin is combined with lamotrigine, the dosage of lamotrigine will need to be increased by 125% (ie, more than doubled). An equivalent dosage of lamotrigine in combination with phenytoin (without valproate) is therefore approximately 5 to 6 times the dosage with valproate (without an EIAED). When carbamazepine is combined with lamotrigine, the lamotrigine dosage will need to be increased by 30% to 50% compared with monotherapy, or 3 times the dosage administered when lamotrigine is combined with valproate (without an EIAED). When an EIAED and valproate are combined with lamotrigine simultaneously, their effects will cancel each other out, or the inhibitory effect of valproate will be somewhat stronger, resulting in a need for a mild decrease in lamotrigine dosage. Co-medication with oxcarbazepine may increase lamotrigine CL modestly, although additional larger studies are needed to confirm and quantify this effect. The effect of felbamate is minor and not clinically significant. None of the other newer AEDs (clobazam, gabapentin, levetiracetam, topiramate, vigabatrin, or zonisamide) have significant pharmacokinetic interactions with lamotrigine. The overall clinical significance of lamotrigine serum concentrations has been demonstrated recently, with lamotrigine tolerability highly correlated with lamotrigine serum concentration.15 Given this relationship, the effect of comedication on lamotrigine CL can be important for clinical care.

Accepted for Publication: December 13, 2004.

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Financial Disclosure: Dr Resor has received consulting fees from Abbott Laboratories, Eisai, Shire, and MedPointe; and speaker fees from GlaxoSmithKline. Dr Hirsch has received research support or other compensation from Eli Lilly, GlaxoSmithKline, Novartis, Ortho-McNeil, UCB Pharma, Eisai, and MedPointe.

Funding/Support: The Columbia Comprehensive Epilepsy Center AED database is supported by Eli Lilly, Novartis, GlaxoSmithKline, Ortho-McNeil, UCB Pharma, and Pfizer.

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