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Association between antiepileptic drug dose and long-term response in patients with refractory epilepsy

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ABSTRACT

Seizures in patients with medically refractory epilepsy remain a substantial clinical challenge, not least because of the dearth of evidence-based guidelines as to which antiepileptic drug (AED) regimens are the most effective, and what doses of these drugs to employ. We sought to determine whether there were regions in the dosage range of commonly used AEDs that were associated with superior efficacy in patients with refractory epilepsy. We retrospectively analyzed treatment records from 164 institutionalized, developmentally disabled patients with refractory epilepsy, averaging 17 years of followup per patient. We determined the change in seizure frequency in within-patient comparisons during treatment with the most commonly used combinations of 12 AEDs, and then analyzed the response to treatment by quartile of the dose range for monotherapy with carbamazepine (CBZ), lamotrigine (LTG), valproate (VPA), or phenytoin (PHT), and the combination LTG/VPA. We found that of the 26 most frequently used AED regimens, only LTG/VPA yielded superior efficacy, similar to an earlier study. For the monotherapies, patients who were treated in the lowest quartile of the dose range had significantly better long-term reduction in seizure frequency compared to those treated in the 2nd and 3rd quartiles of the dose range. Patients with paired exposures to CBZ in both the lowest quartile and a higher quartile of dose range experienced an increase in seizure frequency at higher doses, while patients treated with LTG/VPA showed improved response with escalation of LTG dosage. We conclude that in this population of patients with refractory epilepsy, LTG/VPA was the most effective AED combination. The best response to AEDs used in monotherapy was observed at low dosage. This suggests that routine exposure to maximally tolerated AED doses may not be necessary to identify those patients with drug-resistant seizures who will have a beneficial response to therapy. Rather, responders to a given AED regimen may be identified with exposure to low AED doses, with careful evaluation of the response to subsequent titration to identify non-responders or those with exacerbation of seizure frequency at higher doses.

1. Introduction

Medically refractory epilepsy, defined as continuing seizures despite adequate trials of at least two antiepileptic drugs (AEDs), remains a significant health burden, affecting one-third of the approximately three million people in the US with epilepsy [1]. Despite the prevalence of refractory epilepsy, there are few evidence-based guidelines for its optimal treatment. Most prospective studies have focused on the initial monotherapy of new-onset epilepsy [2–5]. The American Academy of Neurology has published a consensus statement assessing the efficacy of individual AEDs when used as adjunctive therapy in refractory epilepsy, but no guidelines have been issued on the comparative efficacy of AEDs, either used as monotherapy or in combination [6]. Thus neurologists and other clinicians have little guidance but their own experience as to which AEDs are most effective in refractory epilepsy, and what doses to employ.

In a previous study, we addressed the question of the comparative efficacy of AED regimens in an analysis of treatment records from developmentally disabled patients at two Washington State institutions [7]. This unique database recorded the monthly convulsive seizure occurrences in a population of 146 patients, the AEDs used, and their daily dosages. A strength of this database was its extended longitudinal followup, averaging at that time 12 years per patient, with analysis of the eight most frequently used AEDs in regimens of as many as three drugs given at a time. We analyzed the comparative efficacy of differing regimens in within-patient comparisons, thus normalizing for inherent

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differences in seizure frequency among patients. The principal conclusion of this study was that only one AED regimen, the combination of lamotrigine (LTG) and valproate (VPA), demonstrated significant superiority in antiepileptic efficacy. The efficacy of LTG and VPA together greatly exceeded the sum of the efficacies of the component drugs used in monotherapy, and it was suggested that this represented pharmacodynamic synergy, that is, superior efficacy based on as yet unclear cellular or molecular mechanisms of action of the two drugs. Other, more focused studies have also supported the superiority of the LTG/VPA combination [8,9].

Our prior study analyzed AED efficacy without reference to the dosages used. This leaves open the question of whether some AEDs, even if failing to show overall superior efficacy, might be more effective when used in some region of their usual range of daily doses. Common clinical practice is to introduce an AED and escalate dosage to maximal tolerated levels while assessing response. In new-onset epilepsy, however, several studies have shown that the majority of patients who will become seizure-free do so at low doses of AEDs, and that the benefits of further dose escalation are modest [10,11]. Outside of clinical trials, there is a paucity of studies examining the relationship of AED dose and long-term response to therapy in patients with refractory epilepsy.

To address these questions, we first re-analyzed the overall efficacy of frequently used AED regimens using an expanded database comprising the responses to 12 different AEDs alone and in combination over an average of 17 years of followup per patient. We then analyzed the efficacy of the four AEDs most frequently used in monotherapy in our database (carbamazepine [CBZ], VPA, phenytoin (PHT), and LTG), as well as the combination LTG/VPA, with respect to daily dosage by dividing the entire range of daily dosages into quartiles, and determining the comparative efficacy in each dosage quartile for the AED regimens studied. This allowed us to determine how AED efficacy varied with dosage in a retrospective analysis.

2. Material and methods

2.1. Data collection

We obtained epilepsy treatment records for 164 developmentally disabled adults residing at two state-run institutions, the Fircrest Residential Habilitation Center in Shoreline, WA (86 patients) and the Rainier Residential Habilitation Center in Buckley, WA (78 patients). Approval was obtained from the Washington State Institutional Review Board allowing records-based research without patient consent, owing to the patients' diminished cognitive status. Records dating from 1980 to 2015 documented monthly seizure occurrence (primarily convulsive seizures) observed by nursing staff, AED dosages, and basic demographic and diagnostic data. A rotating staff of consulting neurologists who specialized in epilepsy (including author N.P.P.) made epilepsy diagnoses and treatment recommendations. Treatment decisions as to AED regimen composition, dosage level, and rate of introduction of each AED had been made according to each clinician's preferences, and not according to any formal protocol.

Patients included in the study were diagnosed with epilepsy and their seizures were medically refractory, defined as at least one seizure per year despite at least two different treatment trials with AEDs. We studied the 12 most frequently used AEDs as shown in Table 1. We excluded patient data in months with exposure to AEDs other than the study AEDs; months with exposure to more than three concurrent AEDs; months where AED dose was not constant; or data obtained after epilepsy surgery or vagal nerve stimulator implantation. We only analyzed data where there was at least four months of exposure to a given AED combination to avoid the variability inherent in short-term trials where AEDs were likely discontinued for tolerability issues.

Table 1
Antiepileptic drug exposures in the study population including both monotherapy and polytherapy exposures. LTG, VPA, CBZ, and PHT were the most frequently used AEDs.

AED	Abbreviation	No. of patients exposed
Lamotrigine	LTG	128
Valproate	VPA	128
Carbamazepine	CBZ	126
Phenytoin	PHT	95
Topiramate	TPM	87
Levetiracetam	LEV	78
Gabapentin	GBP	59
Phenobarbital	PB	59
Oxcarbazepine	OXC	45
Lacosamide	LAC	38
Zonisamide	ZNS	36
Pregabalin	PGB	17

2.2. Analysis methods

We calculated the average seizure frequency (seizures/month) during the entire time of exposure to each AED combination. Comparisons of efficacy for different AED regimens were calculated as within-patient ratios of the average seizure frequency on that index regimen divided by the baseline average seizure frequency. This baseline seizure frequency was calculated as the average seizure frequency on all other AED regimens to which the patient had been exposed, irrespective of when the exposure to the index regimen occurred; that is, the baseline average included AED exposures potentially both before and after exposure to the index regimen. This seizure frequency ratio (SFR) of index/baseline seizure frequency provided a within-patient metric of AED regimen efficacy that normalized for differences in seizure frequency among patients. We also calculated SFR for each index regimen subdivided by quartile of dosage range: we averaged seizure frequency during exposure to the index AED only for the months when the drug was given in the specified quartile of daily dosage, and compared to the baseline on all other AED regimens except for the index regimen. To make our results comparable to the metric usually reported in AED clinical trials, we report the percent reduction in normalized seizure frequency as $(1\text{-}SFR) * 100$. For AED trials where no seizures were recorded, seizure frequency was set as: 1 / (number of months of treatment with that regimen). This avoids the possibility of division by zero in calculations of the ratio of seizure frequencies between two regimens. (For example, in a 12-month trial with no seizures, seizure frequency was set as 0.083). Statistics on SFR data were performed after log-transformation of the data and are expressed as means $\pm$ 95% confidence intervals (CIs). We used log-transformation of SFR statistics so as to provide a metric that was symmetrical around $SFR = 1$ (representing no change); that is, so that small SFRs (say, 0.1, reflecting a highly effective trial) would be equally weighted against highly ineffective trials where SFR was large (say, 10). After log-transformation, SFRs for all AED regimens were distributed normally, allowing use of parametric statistics. Statistics on demographic data are expressed as means $\pm$ standard errors. Statistical significance was calculated using one-way ANOVA with Tukey post-hoc tests, or with one-sample *t*-tests. Significance was set at $\alpha = 0.05$.

3. Results

3.1. Comparative efficacy of commonly used AED regimens

We sought to extend our prior study on the comparative efficacy of AEDs used in a developmentally disabled patient population with refractory epilepsy. The demographic characteristics of this population are shown in Table 2. The patients were characterized as having developmental disability largely of unknown cause, with a predominance of