Seizures in patients with glioma treated with phenytoin and levetiracetam

Clinical article

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Object. Second-generation antiepileptic drugs (AEDs) are increasingly used in the care of patients with glioma. There is little data on how this practice compares with the use of traditional AEDs in this population. This noninferiority analysis compares seizure outcomes and side effects in patients with glioma treated with phenytoin and levetiracetam monotherapy.

Methods. The authors retrospectively reviewed the records of 500 consecutive patients with glioma who were treated in clinical trials from 2001 to 2008 at the Mayo Clinic campuses. To be eligible for the study, these patients had to have had at least 1 clinical seizure and to have undergone follow-up for at least 6 months. Seizure outcomes, defined by the occurrence of a second seizure, time to second seizure, and seizure frequency, along with AED side effects, were compared between cohorts treated with phenytoin or levetiracetam.

Results. Seventy-six patients were identified, 25 treated with phenytoin and 51 with levetiracetam. Sixty-four percent of the patients had a Grade 4 astrocytoma. There was no difference in seizure outcome between the phenytoin and levetiracetam groups when comparing time to second seizure (p = 0.584), second seizure rates (p = 0.561), and average seizures per month (p = 0.776). When adjusting for age, sex, type of seizure, type of glioma, and dosage using univariate and multivariate models, there were no differences between the treatment groups and none of these covariates were statistically significant for explaining the second seizure rates between treatment groups (all p values > 0.05). The incidence of side effects in the levetiracetam group was 6% versus 20% in the phenytoin group (p = 0.106). Additionally, 36% of the patients in the phenytoin group had dose adjustments unrelated to breakthrough seizures compared with only 10% in the levetiracetam group (p = 0.010).

Conclusions. In this study, patients with glioma treated with levetiracetam and phenytoin had similar seizure control. Patients treated with levetiracetam experienced fewer side effects and required fewer dose adjustments than patients treated with phenytoin. Levetiracetam is a safe, effective, and preferred alternative for seizure management in patients with glioma. (DOI: 10.3171/2010.5.JNS091367)

KEY WORDS • glioma • seizure • levetiracetam • phenytoin • antiepileptic drug

Seizures are a common source of morbidity in patients with glioma. Patients with high-grade glioma tend to have a lower seizure burden than patients with low-grade glioma, ranging between 30% and 70%, respectively.¹⁷,¹⁵,²⁰,²⁶ The general approach in treating seizures in patients with glioma, as for all patients with epilepsy, is to treat using a single AED at the lowest dose that effectively controls seizures followed by 1 or 2 serial monotherapy trials as necessary. Treatment with multiple AEDs is generally reserved for refractory cases. In patients with glioma, incomplete seizure control is a frequent concern.²¹

First-generation AEDs such as phenytoin, carbamazepine, valproic acid, and phenobarbital have been used to treat seizures in patients with glioma. These agents are known to cause a higher incidence of side effects in patients with glioma than in other patients with seizures.²³,¹⁴ Phenytoin has been a traditional first-line therapy, but it can be associated with intolerable side effects, and importantly, may alter the metabolism of chemotherapeutic agents, corticosteroids, and several other medications. This poses numerous problems for the care of these patients and complicates the development of novel therapies.

Second-generation AEDs such as levetiracetam (UCB Pharma, Inc.) have more favorable pharmacokinetics facilitating ease of use with a lesser incidence of side effects. Levetiracetam is not hepatically metabolized but is excreted mostly unchanged renally. There are no known drug interactions with levetiracetam, and it has gained increasing favor in neurooncology practices. Newton and...
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colleagues\textsuperscript{21} looked at the efficacy and tolerability of levetiracetam as an adjunct AED in patients with primary and metastatic brain tumors. They showed that 90\% of their patients received benefit after adding on levetiracetam to an existing AED regimen, with 59\% of the patients experiencing complete seizure control.

There are no reports comparing the efficacy and tolerability between levetiracetam and phenytoin monotherapy in patients with glioma and seizures. In this paper, we report a noninferiority comparison of seizure outcomes and side effects in 2 cohorts of patients with glioma treated with phenytoin or levetiracetam.

Methods

Data Collection

From our database of 500 patients enrolled in clinical trials from 2001 to 2008, we retrospectively reviewed the records of all patients treated at any of the 3 Mayo Clinic campuses who had pathologically proven glioma and seizures. Patients were added to the study from these clinical trials to ensure adequate follow-up. All tissue obtained by biopsy procedure or resection, as well as diagnoses, were confirmed by a Mayo neuropathologist. All inpatient and outpatient neurological, neurosurgical, and neurooncological notes were reviewed. Demographics, tumor type, date of first seizure, AED, initial dose of AED, time to next seizure, total seizures, dose adjustment for seizures, dose adjustments unrelated to seizure control, side effects were recorded.

Patient Characteristics

Study participants were required to have had at least 1 clinical seizure, complete documentation of clinical course for at least 6 months, and initial monotherapy with either levetiracetam or phenytoin. The minimum 6-month clinical course was defined by the date of the initial surgery as time zero. Defining this date ensured a uniform patient population, because patients had their first seizure at various times throughout their clinical courses. All patients were required to consent to use of their records for research.

Seizure outcomes and side effects were compared between the 2 cohorts. The primary outcome was seizure treatment efficacy as measured by time to second seizure and overall seizure frequency. The first seizure was defined as time zero for measuring time to next seizure. The secondary outcomes were side effects, nonseizure-related dose adjustments, and 30-day postoperative seizure rates.

Statistical Analysis

The proportions of patients experiencing a second seizure were compared between the groups of patients receiving levetiracetam and phenytoin using a traditional chi-square test of proportions to test for differences between the proportions. A test of proportion equivalence was also conducted to test if the proportion of patients with second seizures in the levetiracetam group was no more than 15 percentage points higher than in the phenytoin group.\textsuperscript{\textdagger} The occurrence of second seizures in the groups of patients taking levetiracetam and phenytoin was also compared using univariate Cox proportional-hazards models and multivariate logistic models. In the multivariate analysis, occurrence of second seizures was compared while adjusting for age, sex, type of surgery, type of seizure, dose of drug, and patient tumor type.

The time to second seizure was calculated and compared between the groups of patients taking levetiracetam and phenytoin using a 2-sample rank-sum test. The occurrence of side effects and nonseizure-related dose adjustments was determined for each patient and the rates of occurrence were compared between the 2 groups of patients using chi-square tests of proportions.

Results

Seventy-six patients were identified, 25 treated with phenytoin and 51 with levetiracetam. Patient demographics and clinical characteristics are outlined in Table 1. Sixteen patients in the levetiracetam cohort were initially treated with phenytoin for a short time interval (<3 weeks). Five of these 16 patients were switched to levetiracetam due to side effects from phenytoin, and the remaining 11 patients were switched due to clinician preference. One patient was initially treated with levetiracetam for a short time and switched to phenytoin due to side effects. These brief exposures were not considered long enough to have influenced analysis of outcome over 6 months' subsequent observation, and none of these patients experienced their second seizures before being switched from the first to the second drug. Forty-nine patients (64\%) had Grade 4 astrocytoma, and 27 (36\%) had lower grade gliomas. In the Grade 4 astrocytoma cohort, median follow-up time was 18 months (range 6–96 months), and in the lower grade glioma cohort, 38 months (range 9–78 months).

The surgical approach and the lobar and cortical distributions of tumors were approximately equal between cohorts. Similarly, the types of seizures were equally distributed. Approximately equal percentages of phenytoin- and levetiracetam-treated patients underwent biopsy versus resection (approximately 25\% underwent biopsy in both groups vs approximately 75\% who underwent resection in both groups). In all but 1 case some component of cerebral cortex was involved by the tumor. A slightly greater number of levetiracetam-treated patients had frontal/temporal tumor, but this was not statistically significant. In all patients who underwent resection, the extent of resection could only be characterized as maximally safe, and at our institution with a relatively uniform surgical practice, only those patients with satisfactory performance status for whom surgery could result in meaningful cytoreduction with acceptable risk underwent...
operations. The number of Grade 2 and Grade 3 patients with radiographically confirmed resection of more than 90% of all T2 signal abnormality could not be accurately verified, but was considered too small to be a variable in this analysis.

The proportions of patients with second seizures were equivalent between the levetiracetam and phenytoin groups (p = 0.033; test of equivalence using a maximum difference of 15 percentage points higher second seizure rate for the levetiracetam group compared with the phenytoin group). When adjusting for age, sex, type of seizure, type of glioma, and dosage using univariate and multivariate models, there were no differences between the treatment groups and none of these covariates were statistically significant for explaining the second seizure rates between treatment groups (all p values > 0.05).

There was no difference in seizure outcome between the phenytoin and levetiracetam groups when comparing average seizures per month (p = 0.776; Table 2), time to second seizure for the group as a whole (p = 0.584; Fig. 1), or when analyzed separately for Grade 4 astrocytoma (p = 0.796) and lower grade gliomas (p = 0.359; Figs. 2 and 3).

The incidence of side effects in the levetiracetam group was 5.9% versus 20% in the phenytoin group (p = 0.106). Additionally, 36.0% of patients in the phenytoin group had dose adjustments not related to breakthrough seizures compared with only 9.8% in the levetiracetam group (p = 0.010; Table 3).

Sixty-four patients (84%) were taking either phenytoin or levetiracetam at study entry (date of surgery), having already experienced the index seizure or seizures. Five (7.8%) of the 64 patients experienced seizure recurrence in the 30-day postoperative period. Two of these patients were being treated with levetiracetam and 3 with phenytoin. Twelve patients (16%) were not taking an AED during the 30-day postoperative period. Two (17%) experienced their index seizure in this interval. These patients were eventually treated with levetiracetam.

**Discussion**

Seizures frequently complicate the care of patients with glioma. Several studies have shown that prophylactic treatment provides no benefit, and in fact may be harmful. The current standard of practice is to use AEDs only when patients have a clear seizure history.\textsuperscript{14,24} Phenytoin has been commonly used over decades due to its availability in parental form and familiarity among neurosurgeons and neurologists. However, the use of this drug for seizures complicating glioma poses many potential problems for the patient and clinician.

Some of the more common side effects associated with phenytoin include rash, drowsiness, dizziness, and hirsutism. The most feared side effect of phenytoin is Stevens-Johnson syndrome. Toxic levels frequently occur in the therapeutic dose range due to zero-order kinetics. Troublesome difficulties can be encountered in switching between brand name and generic preparations, which

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**TABLE 1: Summary of patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phenytoin Group</th>
<th>Levetiracetam Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>25</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>9 (36)</td>
<td>25 (49)</td>
<td>0.2835</td>
</tr>
<tr>
<td>mean age ± SD in yrs</td>
<td>52.3 ± 12.72</td>
<td>50.5 ± 12.39</td>
<td>0.6905</td>
</tr>
<tr>
<td>age range in yrs</td>
<td>32.0–79.0</td>
<td>25.0–77.0</td>
<td></td>
</tr>
<tr>
<td>Grade 4 astrocytoma</td>
<td>13 (52)</td>
<td>36 (70.6)</td>
<td>0.1117</td>
</tr>
<tr>
<td>progression-free at 12 mos</td>
<td>15 (60)</td>
<td>30 (58.8)</td>
<td>0.9219</td>
</tr>
<tr>
<td>type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>biopsy</td>
<td>6 (24)</td>
<td>13 (25.5)</td>
<td>0.8879</td>
</tr>
<tr>
<td>resection</td>
<td>19 (76)</td>
<td>38 (74.5)</td>
<td></td>
</tr>
<tr>
<td>cortical location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parietal/occipital</td>
<td>7 (28)</td>
<td>7 (13.7)</td>
<td>0.1315</td>
</tr>
<tr>
<td>frontal</td>
<td>18 (72)</td>
<td>44 (86.3)</td>
<td></td>
</tr>
<tr>
<td>tumor location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cortical</td>
<td>24 (96)</td>
<td>51 (100)</td>
<td>0.1505</td>
</tr>
<tr>
<td>deep</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>type of 1st seizure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>complex partial</td>
<td>3 (12)</td>
<td>12 (23.5)</td>
<td>0.4627</td>
</tr>
<tr>
<td>generalized</td>
<td>14 (56)</td>
<td>23 (45.1)</td>
<td></td>
</tr>
<tr>
<td>partial</td>
<td>8 (32)</td>
<td>16 (31.4)</td>
<td></td>
</tr>
</tbody>
</table>

* All values given as number of patients (%) unless otherwise indicated.

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**TABLE 2: Survival to second seizure events and recurrence rates**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Phenytoin Group</th>
<th>Levetiracetam Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>median days to 2nd seizure</td>
<td>730</td>
<td>882</td>
<td>0.584</td>
</tr>
<tr>
<td>no. w/ a 2nd seizure (%)</td>
<td>15 (60)</td>
<td>27 (52.9)</td>
<td>0.561</td>
</tr>
<tr>
<td>mean no. of seizures/mo ± SD</td>
<td>0.076 ± 0.135</td>
<td>0.0755 ± 0.142</td>
<td>0.776</td>
</tr>
<tr>
<td>range of seizures/mo</td>
<td>0.000–0.560</td>
<td>0.000–0.610</td>
<td></td>
</tr>
</tbody>
</table>

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**Fig. 1.** Kaplan-Meier curve showing the percentage of all study patients and all glioma grades who were free from a second seizure in each cohort. LEV = levetiracetam; PHT = phenytoin.
Levetiracetam compared with phenytoin for seizures in glioma

necessitates frequent monitoring of levels and potentially frequent dose adjustments. Moreover, as phenytoin is highly protein bound and can displace other drugs or itself become displaced, monitoring requires measurement of free or unbound drug using assays several times more expensive than total drug level measurements.

Oxidative metabolism through the hepatic P450 (CYP) system is the major route of biotransformation for many AEDs including phenytoin and for many chemotherapeutic agents. The most commonly involved enzymes are CYP 3A4, CYP 2C9, and CYP 2C19. Phenytoin is an enzyme-inducing AED and can potentially increase the clearance of chemotherapeutic agents metabolized through the CYP system including thiotepa, tuxanes and irinotecan, and newer agents such as imatinib, gefitinib, temsirolimus, erlotinib, tipifarnib, and vorinistat.6,11,12,22 The development of novel therapies may be hampered by the requirement of costly Phase I testing of different doses in an otherwise homogeneous group of patients. Conversely, patients taking enzyme-inducing AEDs may simply be denied access to clinical trials of novel therapies. Finally, chemotherapeutic agents can reduce the bioavailability of phenytoin.10 Lower serum concentrations of phenytoin with recurrence of seizures have occurred following administration of several chemotherapeutic agents including nitrosoureas, vinca alkaloids, and cisplatin.5,13,26

In patients with high-grade glioma, a corticosteroid is a typical adjunctive therapy that is required to control vasogenic edema. Interactions between corticosteroids and phenytoin can lead to decreased efficacy of both agents. Dexamethasone is metabolized through CYP 3A4.19,27 The use of enzyme-inducing AEDs such as phenytoin can necessitate using higher doses of dexamethasone to produce the same therapeutic effect and require close monitoring of phenytoin levels.8,17

The second-generation AEDs have revolutionized the treatment of epilepsy. These agents have not necessarily shown greater efficacy than the first-generation AEDs, but have often shown greater tolerability and have allowed the clinician to largely abandon the practice of monitoring drug levels. Many of the second-generation AEDs are not metabolized by the hepatic P450 system and therefore have few, if any, drug interactions. Lastly, some of these agents, including levetiracetam, are now available in reliable generic formulations, improving some of the expense issues encountered in patient care.

The most common side effects of levetiracetam are drowsiness, dizziness, and behavioral side effects. Levetiracetam has first-order kinetics, is excreted through the kidney, and does not have protein binding properties. There are no known drug interactions. Doses as high as 5,000 mg daily are well-tolerated in intractable cases. Thus, it is not necessary to monitor serum levels, except perhaps to monitor compliance concerns.

Seizure frequency and concern over side effects have been shown to be the most significant factors affecting quality of life in previous studies of patients with active epilepsy.2,9 For example, in a large European study, Baker et al.2 showed that 31% of respondents had changed their AED at least once over the past year due to side effects and 44% worried about possible side effects of their AEDs. Lloyd et al.18 found that patients with epilepsy are willing to pay more for AEDs for the benefit of fewer side effects. Auriel et al.1 studied quality of life in patients with well-controlled epilepsy, and found medication side effects to have the most impact.

In this study, patients with glioma treated with leve-
Levetiracetam had similar seizure control as patients treated with phenytoin after adjusting for tumor grade and multiple other variables. Our study had the deficiencies of a retrospective design, and was limited by power to detect small differences in efficacy between the 2 drugs. A larger patient cohort may have shown minor statistically significant differences in efficacy in favor of one of these drugs. Moreover, a sufficiently powered study could potentially address questions regarding seizure outcomes differentially related to particular drug therapies, specific cortical/lobar distributions, extent of resection of contrast-enhancing portions of the tumor, and MR imaging T2 signal change. However, such an undertaking was beyond the scope of this work. For example, with 80% power to detect a 20% difference in the occurrence of a second seizure, 2 equal sample sizes of 215 patients would be required, and with the same power to detect a 25% prolongation in time to second seizure, a study would require 1400 patients. By contrast, our intent was the clear demonstration of noninferiority in seizure management over the first 6 months of the typical evolution of care in patients with all tumor grades and the superiority of levetiracetam in clinically relevant measures that impact quality of life. Clearly, in one important measure (second seizure rate), the apparent equivalence between the 2 drugs met appropriate statistical tests for equivalence.

Our study demonstrated a trend of a higher incidence of side effects in patients treated long-term with phenytoin, although not statistically significant. We were able to show a statistically significant difference in the rate of dose adjustments between phenytoin- and levetiracetam-treated patients reflecting drug level fluctuations, side effects, and toxicity. These occurrences are highly likely to affect intensity of care, costs of care, and quality of life concerns.

An important consideration for the neurosurgical care of patients with glioma in the postoperative period is seizure risk. Our study found that a minority of patients taking either phenytoin or levetiracetam experienced seizures in the postoperative period. The percentage of patients with postoperative seizures in our study is lower than what has been reported.23,25 The low incidence of seizures in the levetiracetam-treated group in the first 30 days following surgery is an important finding for the routine neurosurgical treatment of these patients.

Our patients with Grade 4 tumors demonstrated relatively favorable overall survival. Jaeckle et al.16 similarly noted that patients with high-grade glioma treated with AEDs may have longer overall survival. There is no clear explanation for this observation presently. Future studies could potentially correlate the incidence of seizures with contemporary markers of outcome for primary versus secondary glioblastoma, such as mutation in the gene encoding isocitrate dehydrogenase. It is plausible that seizures may occur more frequently in patients with secondary glioblastoma, a prognostically more favorable group.28

Conclusions

Levetiracetam appears to be a safe, effective, and pre-ferred alternative for postoperative and long-term seizure management in patients with glioma. Levetiracetam has equal efficacy to phenytoin for seizure control, a similar and possibly more favorable side effect profile, and a reduced need to make dose adjustments. Levetiracetam has no potential for interactions with chemotherapeutic agents or corticosteroids, and simplifies eligibility considerations for clinical trials.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Lachance, Merrell. Acquisition of data: Lachance, Merrell. Analysis and interpretation of data: all authors. Drafting the article: Lachance, Merrell, Anderson. Critically revising the article: Lachance, Merrell, Anderson. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Lachance, Anderson. Administrative/technical/material support: Lachance, Meyer. Study supervision: Lachance.

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11. Drappatz J, Schiff D, Kesari S, Norden AD, Wen PY: Medical supervision: Lachance. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Lachance, Anderson. Administrative/technical/material support: Lachance, Meyer. Study supervision: Lachance.
12. Drappatz J, Schiff D, Kesari S, Norden AD, Wen PY: Medical supervision: Lachance. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Lachance, Anderson. Administrative/technical/material support: Lachance, Meyer. Study supervision: Lachance.
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