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A Prospective Randomized Trial of Peri-Operative Seizure Prophylaxis in Patients with Intraparenchymal Brain Tumors

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Abstract

Object—Seizures are a potentially devastating complication of surgical resection of brain tumors. Consequently, many neurosurgeons administer prophylactic anti-epileptic drugs (AEDs) in the peri-operative period. However, it is currently unclear whether peri-operative AEDs should be routinely administered to patients with brain tumors who have never had a seizure. Consequently, we conducted a prospective, randomized trial examining the use of phenytoin for post-operative seizure prophylaxis in patients with supratentorial brain metastases or gliomas undergoing surgical resection.

Method—Patients with brain tumors (metastases or gliomas) who did not have seizures and who were undergoing craniotomy for tumor resection were randomized to receive either phenytoin for 7 days following tumor resection (prophylaxis group) or no seizure prophylaxis (observation group). Phenytoin levels were monitored daily. Primary outcomes were seizures and adverse events (AEs). Using an estimated seizure incidence of 30% in the observation arm and 10% in the prophylaxis arm, a type I error of 0.05 and a type II error of 0.20, a target accrual of 142 patients (71 per treatment arm) was planned.

Results—The trial was closed before completion of accrual because Bayesian Predictive Probability analyses performed by an independent Data Monitoring Committee indicated that the probability that at the end of the study prophylaxis would prove superior to observation was 0.3% and the probability that there would be insufficient evidence at the end of the trial to choose either arm as superior was 99.7%. At the time of trial closure, 123 patients (77 metastases, 46 gliomas) were randomized, with 62 receiving 7-day phenytoin (prophylaxis group) and 61 receiving no-

prophylaxis (observation group). The incidence of all seizures was 18% in the observation group compared with 24% in the prophylaxis group ($p = 0.51$). Importantly, the incidence of early seizures (<30 days after surgery) was 8% in the observation group compared with 10% in the prophylaxis group ($p = 1.0$). Likewise, the incidence of clinically significant early seizures was 3% in the observation group and 2% in the prophylaxis group ($p = 0.62$). The prophylaxis group experienced significantly more AEs (18% vs. 0%, $p = <0.01$). Therapeutic phenytoin levels were maintained in 80% of patients.

Conclusions—The incidence of seizures after surgery for brain tumors is low (8%, 95%-CI 3-18%) even without prophylactic AEDs, and the incidence of clinically significant seizures is even lower (3%). In contrast, routine phenytoin administration is associated with significant drug-related morbidity. Although the lower-than-anticipated incidence of seizures in the control group significantly limited the power of the study, the low baseline rates of perioperative seizures in patients with brain tumors raises concerns about the routine use of prophylactic phenytoin in this patient population.

Keywords

phenytoin; seizure prophylaxis; glioma; brain metastasis; tumor resection

Introduction

Seizures are a potentially devastating complication of surgical resection of brain tumors, often worsening existing neurological deficits, producing new deficits, and prolonging the length of hospitalization after brain tumor surgery.¹² Post-operative seizures may result in intra-ictal injury, decreased cognitive function, and even death.¹ Most states in the USA suspend driving privileges after a seizure, significantly limiting quality of life after surgery.

The incidence of seizures in patients with brain tumors is reported to be approximately 30%.^{3, 4, 6, 15, 16} Consequently, many neurosurgeons routinely administer prophylactic anti-epileptic drugs (AEDs) in the peri-operative period to patients who have never had a seizure and who are undergoing brain tumor resection in order to prevent the adverse effects of a post-operative seizure. Indeed, in a recent survey conducted by Glantz et al.,¹⁰ 81% of neurosurgeons reported that they prescribed prophylactic AEDs to patients without a history of seizures. Phenytoin is the most commonly administered anticonvulsant, although recently other anticonvulsants, particularly levetiracetam, have been increasingly prescribed.

Temkin et al.²¹ studied the efficacy of phenytoin in the prevention of post-traumatic seizures in a prospective, randomized, double-blind study of 404 patients with serious head injuries, and found a significant beneficial effect of phenytoin against seizures during the first week after head trauma, although continued administration of phenytoin beyond seven days did not prevent late seizures. This study suggested that seven days of phenytoin prophylaxis is sufficient to prevent early seizures in this patient population. However, the effect of AEDs in trauma patients may not readily apply to patients undergoing surgery for brain tumors. North et al.¹⁵ performed a randomized study of seizure prophylaxis with phenytoin after supratentorial neurosurgery for a variety of indications in 281 patients, only 45 of whom underwent craniotomy for cerebral metastases or gliomas. The authors observed fewer

seizures in the patients given phenytoin prophylaxis, and the most protective effect of the drug was observed in the first 30 days, suggesting efficacy for short-term prophylaxis. However, patients with diagnoses other than brain tumors were included in this study. Two other clinical trials have focused on seizure prophylaxis only in patients with brain tumors, but these studies did not specifically address peri-operative prophylaxis^{8,10}. Interestingly, no beneficial effects of seizure prophylaxis were observed in these clinical trials.

Because there is no study that has specifically focused on perioperative seizures in patients with brain tumors, it is currently unclear whether prophylactic, peri-operative AEDs should be routinely administered to patients with brain tumors who have never had a seizure and who are undergoing surgical resection of their tumor. Therefore, in order to evaluate the efficacy and safety of peri-operative phenytoin prophylaxis in this patient population, we conducted a prospective, randomized study of patients with gliomas or cerebral metastases randomized to receive or not receive phenytoin for the initial seven-day period following tumor resection.

Methods

Study Design

Eligible patients with either metastatic brain tumors or gliomas based on their pre-operative diagnosis as determined either by stereotactic biopsy or MRI were enrolled into the study. Patients were randomized to receive either short term (7 day) AED prophylaxis with phenytoin (prophylaxis group) or not to receive prophylaxis (observation group). The primary endpoint was the occurrence of a seizure, and the secondary endpoint was the occurrence of adverse reactions to phenytoin. Informed consent and Institutional Review Board (IRB) approval were obtained per the guidelines of the University of Texas M. D. Anderson Cancer Center.

Eligibility Criteria

Patients with intraparenchymal, supratentorial brain tumors either proven by biopsy to be a brain metastasis or a glioma, or with compelling CT or MRI evidence of metastasis or glioma were selected for this study. All patients had to be previously untreated, with the exception of whole brain radiation therapy greater than four weeks prior to enrollment, and all patients had to undergo craniotomy for resection of their brain tumor, with the goal of maximal safe resection of the targeted lesion. All eligible patients also had to have had no seizure on presentation prior to entering the study, and not have received any prophylactic AED therapy prior to enrollment. Other inclusion criteria were: age 8 years or older, Karnofsky Performance Scale (KPS) score $\geq$ 70, and normal electrolytes (Na, K, Mg, PO₄, and Ca within 10% of institutional normal) prior to surgery. Exclusion criteria were a history of epilepsy or seizures, solely posterior fossa tumors, the existence of any other past or concomitant intracranial pathology, prior toxicity to phenytoin, whole brain radiation therapy within 4 weeks of enrollment, any previous surgical resection other than stereotactic biopsy, leptomeningeal disease, elevated liver enzymes (AST, ALT and bilirubin $\leq$ 3 times institutional normal), lactation and pregnancy (diagnosed by β -HCG $\leq$ 5 mIU/mL).

Patient Evaluation and Follow-up

All patients received a pretreatment evaluation including a complete medical history and general physical exam, assessment of seizure and anticonvulsant history, KPS, neuro-cognitive assessment, MRI of the brain without and with contrast, and measurement of CBC, platelets, electrolytes, Ca, Mg, PO₄, LFTs. Patients with childbearing potential also had measurement of serum beta-HCG.

All patients had a post-operative MRI scan within 72 hours of surgery. Follow-up evaluations were conducted daily for up to 3 days after surgery while patients were in hospital, then at postoperative day (POD) 8. Subsequent follow-up was then conducted every 2 to 3 months up to 12 months. At each follow-up evaluation, history of any new seizures was recorded, and serum electrolytes measured. In addition, at the 8 day and 1 month evaluations, patients randomized to the phenytoin arm were assessed for signs and symptoms of phenytoin toxicity, including nystagmus, blurred vision, ataxia, drowsiness, rash, fever, hirsutism, acne, gingival hyperplasia, hepatosplenomegaly, arthralgia, and eosinophilia, and liver function studies conducted. Serum phenytoin levels were also measured daily in the morning while patients were in the hospital and at the day 8 follow-up. Patients with evidence of phenytoin toxicity and normal phenytoin levels also had their albumin levels measured.

Adverse events were recorded and graded on severity using the National Cancer Institute Common Toxicity criteria on a scale from 1 to 5 (1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, 5 = lethal). Events in grades 1 or 2 were classified as minor, while events in grades 3, 4, or 5 were classified as major, and corresponded to complications with significant negative impact on patient outcome and/or course of treatment. Each adverse event was reviewed by the primary investigator and determined to be unrelated, possibly, probably, or definitely related to phenytoin treatment.

Phenytoin Administration

Patients randomized to the observation group did not receive any phenytoin before or after surgery until the end of their participation in the study, defined by death, definite seizure, or at the 12-month follow-up evaluation, or if informed consent was withdrawn.

Patients randomized to the prophylaxis group received a loading dose of Phenytoin (15mg/kg IV) in the operating room prior to commencing the craniotomy, followed by 100 mg every 8 hr (orally or intravenously) for 7 days post-operatively, and then tapered starting at post-operative day 8 with a 100 mg dosage decrease every two days until discontinuation. Phenytoin levels were drawn immediately after surgery and then daily in the morning while patients were in hospital. Additional boluses and/or changes in daily dosing were made as needed per the primary physician's judgment, with a therapeutic goal of maintaining phenytoin levels between 10 and 20 mg/L. Serum phenytoin levels were also measured at the day 8 follow-up.

Seizure Determination

Patients were instructed to contact the study nurse when they had a suspected new seizure. Seizures were diagnosed primarily by clinical manifestations including involuntary movements, alteration in consciousness, or abnormal motor, sensory, or psychosensory phenomena. An independent senior neurologist (AF), blinded to the patients' treatment, confirmed the occurrence of every seizure. If a seizure could not be definitely diagnosed on clinical grounds alone, an electroencephalogram (EEG) was performed within 24h of event occurrence to confirm the diagnosis. If the EEG showed evidence of interictal or seizure activity, the event was upgraded to a definite seizure. If the EEG was not done within 24 hours or if the EEG was not diagnostic, the event was classified as no seizure or possible seizure as determined by the blinded neurologist.

Seizures were classified as "early seizures" if they occurred within 30 days of surgery. This period of time corresponded to the period of post-operative phenytoin administration, through to the completion of the taper, and including the first 2 weeks following complete cessation of anti-epileptic medication. Intraoperative seizures that occurred during direct cortical stimulation, secondary to the application of an electrical current, were not considered an endpoint to the study.

Seizures was classified as clinically significant if the sequelae of the seizure resulted in neurological deficits, an admission to hospital, or alteration of the patient's course in hospital, including transfer from the post-operative nursing unit to the intensive care unit (ICU), a delay in transfer out of the ICU to the post-operative nursing unit, a delay in transfer from the post-operative nursing unit to inpatient rehabilitation, or a delay in discharge from hospital.

Serum electrolytes, Ca, Mg, and PO₄ were drawn within 24h of every seizure occurrence. Patients taking phenytoin also had determination of serum drug levels and liver function tests. All definite seizures were treated as deemed appropriate by the attending physician, and considered failures of prophylaxis.

Statistical Analysis

Using an estimated seizure incidence of 30% in the no prophylaxis arm and 10% in the prophylaxis arm, and a type II error of 0.20, a target accrual of 142 patients (71 per treatment arm) was planned. This accrual ensured that our trial would have a power of at least 0.80, as determined by Fisher's exact test, to detect a clinically meaningful two-thirds (67%) reduction in the odds of seizure in the phenytoin prophylaxis group (i.e. a reduction of seizure incidence from 30% to 10%). Primary analysis was conducted on an intent-to-treat basis. Statistical analysis with Fisher's exact test was performed using SPSS software. A p-value of <0.05 was considered statistically significant. Seizure frequency rates for each arm were also compared in an odds-ratio analysis. "Freedom from seizure" curves were generated by the Kaplan-Meier method and compared with a log-rank test. Peri-operative "freedom from seizure" was defined as the number of days from randomization to the incidence of the first seizure, or to 30 days in the case of seizure-free patients.

Decision to Terminate the Trial

At 6 years when 123 patients had been enrolled, just 19 short of the goal, the trial was closed to further accrual because an interim futility analysis using Bayesian Predictive Probabilities performed by an independent Data Monitoring Committee (DMC) demonstrated a low likelihood that either the observation or phenytoin prophylaxis group would be superior if the study was completed to its full sample size (Appendix). At the time of this analysis, there were 11 seizures in the observation arm and 15 seizures in the phenytoin arm. Therefore, the Bayesian Predicted Probability that, at the end of the study, it would be concluded that prophylaxis reduced the rates of seizures compared with observation was only 0.003. In addition, the probability that there would be insufficient evidence at the end of the trial to show that one treatment was superior to the other was 0.997. In other words, it was extremely unlikely that the proposed difference in seizure rates (i.e. reduction from 30% to 10%) would be realized. Therefore, the trial was closed before reaching its planned accrual of 142 patients.

Because the detected incidence of early seizures was only 8% in the control group of our study (significantly less than our estimated rate of 30%), the true power of our study to detect a clinically important difference (2/3 reduction in post-surgical, 30-day, seizure incidence) based on our accrual of 123 patients was only 19%. It is important to note that the main cause of this limited power was the lower-than-expected incidence of seizures not poor accrual (we only needed 19 more patients to reach our accrual goal). In fact, with an 8% incidence of early seizures in the control (observation) arm, a type I error of 5% and a power of 80%, over 700 patients would have been needed to detect a 2/3 decrease in seizure rate (8% to 3%). To demonstrate smaller reductions of 50%, 40% or 30% would have required even larger numbers of patients (1,204 patients, 2,250 patients and 5,306 patients, respectively). This accrual target was not considered feasible and so the trial was closed.

Nevertheless, we present the results of the 123 patients entered into this trial because to-date this is the first and only clinical trial to focus specifically on peri-operative seizure prophylaxis in patients with brain tumors, the cohort is larger than any other prospective study of seizure prophylaxis in brain tumor patients⁸, and the data provide important prospective information about the actual rates of peri-operative seizures in patients undergoing craniotomy for brain tumors.

Results

Study Population

Patient enrollment continued from July 17, 2000 to February 24, 2006. A total of 123 patients (77 with metastases and 46 with gliomas) were enrolled and randomized. 61 patients were randomized into the observation group (38 with metastases and 23 with gliomas), and 62 patients were randomized into the prophylaxis group (39 metastases and 23 gliomas).

A comparison of patient characteristics between the treatment groups is summarized in Table 1. There were no differences between treatment groups in terms of median age, gender, preoperative KPS, preoperative signs and symptoms, use of direct cortical

stimulation mapping, tumor location, tumor size, number of brain lesions or metastases, or extent of resection.

A summary of the histopathological diagnoses is provided in Table 2. In the metastasis subgroup, tumor types were distributed equally between treatment arms, except that there was a significantly greater incidence of melanoma in the prophylaxis group (36%) than in the observation group (13%, $p = 0.03$). In the glioma subgroup, 80% of tumors were high grade gliomas, while 13% were low grade gliomas. No statistically significant differences in glioma grade or type were observed between treatment groups. Three patients initially included in the glioma subgroup turned out to have a final histopathological diagnosis that was not a glioma. Of these, there was one metastasis, one lymphoma, and one T-cell lymphoproliferative disorder. These three cases were kept in the glioma subgroup for subsequent analysis in keeping with intent to treat protocol.

Seizure Incidence

A total of 26 seizures occurred in the patients in this study (Table 3). Eleven seizures (18%) occurred in the observation group, and 15 (24%) in the prophylaxis group. This difference in rates was not statistically significant ($p=0.51$). Likewise, no significant difference was observed in the incidence of seizures between the observation and prophylaxis groups in separate analyses of the metastasis (15% vs. 13%, $p=1.00$) or glioma (39% vs. 26%, $p=0.53$) subgroups (Table 3).

Seizures were characterized as generalized, simple partial, complex partial, or other. There was no difference between treatment groups with regard to the type of seizure in the whole group ($p=0.60$), or each of the metastasis ($p=0.98$) or glioma ($p=0.47$) subgroups.

A total of 11 patients had “early” postoperative seizures, i.e., within 30 days of surgery, which is the period that encompassed the time of administration and taper of the seizure prophylaxis and the first 2 weeks immediately after cessation of antiepileptic medication. These seizures were likely related to recent surgical resection. Of these early seizures, 5 (8%) occurred in the observation group, and 6 (10%) occurred in the prophylaxis group; this difference was not significant ($p=1.00$). One patient (2%) in the prophylaxis group and two patients (3%) in the observation group had seizures postoperatively on the day of surgery. Of the phenytoin-treated patients who had early seizures, no seizures were reported during the tapering period (POD 8-12), but four patients had seizures in the period between complete cessation of treatment and 30 days. No significant difference was observed in the incidence of seizures between the two treatment groups within the first 24 hours (2% prophylaxis group vs. 3% observation group, $p=0.62$), 3 days (3% vs. 5%, $p=0.68$), 1 week (3% vs. 8%, $p=0.274$) or 30 days after surgery (10% vs. 8% $p=1.00$). The observed odds for an early seizure in the prophylaxis group relative to the observation group was 1.4 (95% CI 0.425 - 4.763). Therefore, a clinically meaningful reduction (defined as 67% in our trial) in the incidence of seizure was not achieved by treatment with phenytoin compared with no drug.

Because the trial endpoint was spontaneous seizures in the postoperative period, patients who had intraoperative seizures during electro-cortical brain mapping were kept in the trial

and evaluated for subsequent seizures. Of the 34 patients who underwent electro-cortical mapping, two patients had a focal intraoperative seizure during cortical stimulation. These stimulation-induced seizures were focal motor seizures involving the contralateral extremity/face during stimulation of the motor cortex. Seizure activity stopped within seconds of cold Ringer's Lactate application over the surface of the stimulated cortex. Both of these patients were in the phenytoin arm and experienced an intraoperative seizure despite therapeutic anti-epileptic levels. One of these patients had an early seizure (two days after surgery), the other a late seizure (84 days after surgery).

Figure 1 shows the actuarial probability of remaining seizure-free in the first 30 days according to treatment group. The prophylaxis group had a mean ($\pm$ SE) "freedom from seizure" of 28.4 ± 0.7 days (95% CI 26.9 to 29.8 days) compared with the observation group, which had a mean "freedom from seizure" of 27.7 ± 1.0 days (95% CI 25.8 to 29.6 days). There was no significant difference in "freedom from seizure" between the two groups as a whole (log rank test $p=0.80$), or in the metastasis (log rank test $p=0.53$) or glioma (log rank test $p=0.48$) subgroups. Across both treatment arms and within the metastasis and glioma subgroups, tumors affecting the frontal and temporal lobes were more likely to produce seizures, although this difference was not found to be statistically significant ($p=0.76$).

A total of 15 patients had "late" seizures, i.e., seizures that occurred more than 30 days after surgery. Whether these seizures were directly related to the tumor resection/craniotomy was difficult to determine because patients received local (radiation) and systemic (chemotherapy) treatments during this time in the course of their disease and because tumor recurrences are also known to produce seizures. In fact, 5 (36%) of these late seizures were associated with unequivocal tumor recurrence. Nevertheless, no significant difference was observed in the incidence of late seizures between the observation and prophylaxis groups in the whole group, and in separate analyses of the metastasis or glioma subgroups (Table 3).

A total of 7 clinically significant seizures occurred in the patients in this study, and 3 clinically significant seizures occurred within 30 days and, therefore were likely due to recent craniotomy. In the first case, a series of generalized seizures occurred over the course of the first few hours immediately after surgery, resulting in increased drowsiness and requiring intubation and transfer to the intensive care unit (ICU). In the second case, seizures on the first post-operative evening in the ICU resulted in a post-ictal hemiparesis, with mild residual weakness still remaining at the time of discharge six days after surgery. In the third case, a seizure occurring two days after surgery resulted in mild weakness that delayed discharge by 1 week. Of these clinically significant early seizures, two occurred in patients in the observation group, and one occurred in the prophylaxis group. Once again, there were no statistically significant differences in the incidence of clinically significant seizures between the observation and the prophylaxis groups, either in the whole group (2% vs. 3%, $p=0.62$), or each of the metastasis (0% vs. 3%, $p=0.31$) or glioma (4% vs. 4%, $p=1.00$) subgroups (Table 3).

Serum Phenytoin Levels

Serum phenytoin levels are shown in Table 4. The loading dose quickly produced therapeutic levels on the day of surgery in 78% of patients, and levels were maintained within target range for the majority of patients (70-80%) in the study through 3 days after surgery. The percentage of patients for whom blood levels were drawn decreased as patients were discharged from the hospital. Nevertheless, drug levels remained high in the patients for whom phenytoin measurements were available. At the conclusion of the week, levels were considerably lower. This phenomenon was noted by Temkin et al. and may be ascribed to the hypermetabolic state of patients and unpredictable kinetics of phenytoin at one week postoperatively,^{11, 21} or partial noncompliance after discharge.

Adverse Events

A total of 20 adverse events that were “possibly,” “probably,” or “definitely” related to seizure prophylaxis occurred within 30 days of surgery, which involved 11 patients (12 events in 7 patients in the metastasis subgroup and 8 events in 4 patients in the glioma subgroup). Of these, a total of 5 major adverse events occurred in 3 patients (4 events in 2 patients in the metastasis subgroup, and 1 event in 1 patient in the glioma subgroup). Adverse events included: rash (4 events), 2 thrombocytopenias (2 events), decreased level of consciousness (1), confusion (2), increased LFTs (4), nausea (1), vomiting (1), dry-itchy skin (1), ataxia (1), photophobia (1), aphasia (2). Among the 5 major adverse events, 2 were gastrointestinal, and 3 were neurological.

A comparison of the number of adverse events within 30 days potentially related to seizure prophylaxis in each treatment group is shown in Table 5. When all the patients were considered, there were significantly more total (18% vs. 0%, $p < 0.01$) and minor (15% vs. 0%, $p < 0.01$) adverse events among the prophylactic group than among the observation group. Differences in the occurrence of major adverse events were not statistically significant, but favored the observation group (5% prophylaxis group vs. 0% observation group, $p = 0.24$). In the metastasis group, there were significantly more total adverse events in the prophylaxis group than in the observation group (18% vs. 0%, $p = 0.01$), but no significant difference in the occurrence of major (5% vs. 0%, $p = 0.49$) or minor (13% vs. 0%, $p = 0.06$) adverse events, although more adverse events occurred in the prophylaxis group. In the glioma subgroup, no significant difference was seen in the occurrence of total (17% vs. 0%, $p = 0.11$), minor (17% vs. 0%, $p = 0.11$) or major (4% vs. 0%, $p = 1.00$) adverse events, but again more adverse events occurred in the prophylaxis group.

Discussion

To our knowledge, this study is the first randomized, prospective clinical trial to specifically examine the perioperative use of prophylactic AEDs in patients with brain tumors without a previous history of seizures and who were undergoing surgical resection. Two prior studies examining the use of prophylactic phenytoin after craniotomy showed efficacy of prophylaxis in reducing the incidence of post-operative seizures, but these trials included patients with a variety of neurosurgical problems, including aneurysms and head trauma, in addition to tumors.^{15,16} Two other studies have explored the use of prophylactic AEDs

exclusively in brain tumor patients, but most of the patients in these studies did not undergo surgical resection. Glantz et al.¹⁰ conducted a randomized, placebo controlled trial using divalproex sodium for seizure prophylaxis in 74 patients with newly diagnosed brain tumors, 25 of whom had surgery, and found that prophylaxis was not effective in preventing seizures. Forsyth et al.⁸ reported a randomized trial of prophylactic AEDs in 100 newly diagnosed brain tumor patients (60 cerebral metastases and 40 primary brain tumors), 39 of whom had a craniotomy for tumor diagnosis, and found no statistically significant difference in seizure incidence and seizure-free survival between patients given AEDs and patients who were observed. This study was terminated early due to lower than expected seizure rates, with the authors reporting that >900 patients would have been necessary for a suitably powered study. Sirven et al.¹⁹ conducted a meta-analysis of randomized control trials of prophylactic AEDs in brain tumor patients conducted between 1996 and 2004 (including the Glantz¹⁰ and Forsyth⁸ trials) using phenytoin, valproic acid, and/or phenobarbital and found no evidence of benefit at 1 week or 6 months in patients with cerebral metastases, gliomas, or meningiomas. Therefore, prophylactic AEDs have consistently failed to demonstrate efficacy in seizure control in newly diagnosed brain tumor patients without prior history of seizures.

Consistent with these results, the prospective randomized trial presented here suggests that the prophylactic use of phenytoin is not effective in preventing seizures in the post-operative period in patients who had never had a seizure and who underwent surgical resection for supratentorial metastases or gliomas. Specifically, we found no statistically significant differences in seizure incidence or “freedom from seizure” in patients treated with phenytoin compared with patients who were observed. Furthermore, patients in the prophylaxis group had a statistically significantly higher incidence of drug-related morbidity. However, our data must be interpreted with caution because our trial, like the study of Forsyth et al.,⁸ was terminated early after interim analyses determined that continued accrual to the goal of 142 patients (19 more than actually accrued) was highly unlikely to demonstrate any statistically significant difference between treatment groups. In other words, even if we accrued all patients to the study we would not have been able to conclude that prophylactic Phenytoin was ineffective in preventing seizures because the actual rates of seizures in the observation group, namely 18% overall and 8% early seizures, were significantly lower than the 30% rate for which the study was powered. In fact, based on an early seizure rate of 8%, over 700 patients would have been needed to be relatively certain (80% power) of a negative result.

Nevertheless, this prospective data is of value because it shows that the incidence of seizures in patients undergoing craniotomy for brain tumor is low, only 8% in the first 30 days after surgery and only 3% for clinically significant seizures. In contrast, side effects of phenytoin are high. Therefore, when taken in the context of other clinical trials, our prospective data raise serious concerns about the routine use of prophylactic phenytoin in patients with brain tumors undergoing craniotomy. Any benefit of prophylactic AEDs in brain tumor patients undergoing surgical resection is likely to be quite small, and leads to the question of whether such a small benefit would be clinically important given that the baseline rates of seizures (even without anticonvulsants) are low. In addition, such a small beneficial effect would only be justified if the side effects of the AED were extremely mild and rare. Because no currently available AED fulfills these criteria, we would suggest that future studies should

focus on identifying the 8% of patients who are at high risk for seizures so that we can specifically target these patients rather than using a global routine administration of anticonvulsants in all patients.

Most of the patients randomized to the prophylactic arm achieved therapeutic blood levels during the first critical days after surgery, with several troughs within target range during the observation period. Indeed, lack of efficacy of phenytoin in preventing early postoperative seizures in this study could not be explained by inadequate dosing, because the average serum drug levels during the 7 day treatment were within therapeutic range in the majority of patients. Nevertheless, it was our experience that attaining adequate drug levels at the end of the week was difficult, despite optimal dosing and frequent monitoring of serum drug concentrations. This phenomenon has been noted in previous studies.^{8, 9, 21} Confounding factors include unpredictable kinetics of phenytoin in the postoperative period,¹¹ hypermetabolism of surgical patients,²¹ and drug interactions with antineoplastic therapy.² In addition, our ability to measure the effectiveness of treatment after post-operative day 3 was limited by difficulties with drawing phenytoin levels after discharge from the hospital. However, despite these limitations, within the patients randomized to the prophylaxis arm, the median number of therapeutic troughs in patients with early seizures as compared with those who did not have a seizure was not statistically significant. Ultimately, these issues are relevant to the “real-world” application of peri-operative prophylaxis. It may be that 19% - 50% of patients with confirmed epilepsy have subtherapeutic levels.¹³

The effectiveness of phenytoin prophylaxis in controlling early seizures in patients with head trauma has been demonstrated in a randomized, double-blinded placebo controlled trial.²¹ Our findings suggest that this result cannot be generalized to the brain tumor population undergoing craniotomy for surgical resection. Therefore, the assumption that the “trauma” associated with craniotomy and tumor resection may increase the risk of seizures in a manner analogous to that observed in traumatic head injury does not appear to be supported by the available evidence. A possible explanation for this observation is that in contrast to the situation in head injury patients where the trauma is uncontrolled, “trauma” associated with surgical resection of a tumor occurs in highly controlled circumstances with the prior administration of general anesthesia and corticosteroids, and with minimal local brain manipulation such that secondary injury and kindling of epileptogenic foci are ameliorated. In this context, the etiologic causes of seizures in brain tumor patients may well be more related to the effects of the tumor mass, and its associated features, such as infiltration of surrounding normal brain, disruption of the blood-brain barrier, and edema. Surgical resection would be expected to reduce the severity of all these factors. Indeed, seizures associated with specific mass lesions are frequently refractory to control by AEDs, and often respond best to surgical resection of the epileptogenic focus, a fact that may explain the lack of efficacy of prophylactic AEDs in the setting of brain tumors. It is possible that the most effective means of seizure control in this patient population is the actual resection of the tumor itself.^{7, 9} In the large retrospective study by Chaichana et al.,⁵ of the 24% of patients who presented with seizures, 77% were seizure free 12 months after surgical resection, and 95% had at least meaningful improvement in seizure control after 12 months.

A major risk of intraoperative cortical mapping is stimulation-induced seizures. Consequently, neurosurgeons may administer prophylactic AEDs in patients undergoing electro-cortical stimulation to prevent an intraoperative seizure during mapping. However, despite therapeutic levels of antiepileptic, intraoperative stimulation-evoked seizures may occur in up to 5-20%.¹⁸ Several retrospective studies have reported rapid and reliable termination of intraoperative seizures with cold LR, without any postoperative deficits or increased seizure frequency.^{17, 20} This technique is utilized commonly at our institution, and many others. There is little evidence that prophylactic AEDs are effective in the prevention of intraoperative seizures. Therefore, given the side-effect profile of AEDs, and the success of cold LR in terminating stimulation-evoked seizures with minimal morbidity, antiepileptic prophylaxis for patients undergoing cortical stimulation may not be warranted. Only a randomized controlled trial on the use of prophylactic AEDs for seizure prophylaxis in brain tumor patients undergoing surgical resection with cortical stimulation mapping would definitively answer this question.

We suspect that our results with phenytoin are generally applicable to all AEDs. In particular, levetiracetam recently has become a popular alternative to phenytoin for seizure prophylaxis, due to a possibly more favorable side effect profile, and lack of drug interactions.¹⁴ A Phase II study with a small number of patients suggests that the use of levetiracetam for seizure prophylaxis in brain tumor patients is “safe and equally effective compared with phenytoin.”¹⁴ A more favorable side effect profile could shift the balance of risk-versus-benefit in favor of use of the prophylactic AED. However, in light of our results, “equally effective compared to phenytoin” begs the question of whether phenytoin, or any prophylactic AED, offers any clinically meaningful benefit at all in the brain tumor population. This is a question that can only be answered definitively with a randomized controlled trial of the use of levetiracetam for seizure prophylaxis in brain tumor patients undergoing surgical resection. However, we are not aware that such a study has yet been attempted.

Conclusion

There is no consensus among neurosurgeons treating patients with brain tumors regarding the use of peri-operative prophylactic AEDs. The low rates of seizures seen in the control arm of this prospective trial raise serious concerns about the routine use of peri-operative prophylactic phenytoin in patients with brain tumors may not be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Kaplan-Meier freedom-from seizure probability according to treatment group. There was no significant difference in early perioperative freedom-from seizure between (A) the two groups as a whole (log rank test $p=0.80$), or in the (B) metastasis (log rank test $p=0.53$) or (C) glioma (log rank test $p=0.48$) subgroups.

Table 1

Baseline characteristics of patients

	Whole Group		p-value	Metastasis Subgroup		p-value	Glioma Subgroup		p-value
	Observe N=61	Prophylaxis N=62		Observe N=38	Prophylaxis N=39		Observe N=23	Prophylaxis N=23	
Median Age (range)	61 (35-84)	56 (16-80)	1.00	59 (41-75)	56 (16-79)	1.00	64 (35-84)	56 (17-80)	1.00
Gender M:F (%M)	30:31 (49%)	37:25 (60%)	0.28	18:20 (47%)	25:14 (64%)	0.17	12:11 (52%)	12:11 (52%)	1.00
Median KPS (range)	90 (70-100)	90 (70-100)	1.00	90 (70-100)	90 (70-100)	1.00	90 (70-100)	90 (70-100)	1.00
No. patients with focal motor, sensory, or speech deficit (%)	20 (33%)	16 (26%)	0.43	12 (32%)	12 (31%)	1.00	8 (35%)	4 (17%)	0.31
Site of tumor			1.00			1.00			1.00
Frontal	21 (34%)	27 (44%)	0.36	13 (34%)	20 (51%)	0.17	8 (35%)	7 (30%)	1.00
Temporal	18 (30%)	16 (26%)	0.69	8 (21%)	8 (21%)	1.00	10 (43%)	8 (35%)	0.76
Parietal	10 (16%)	7 (11%)	0.45	7 (18%)	5 (13%)	0.55	3 (13%)	2 (9%)	1.00
Occipital	11 (18%)	7 (11%)	0.32	9 (24%)	4 (10%)	0.14	2 (9%)	3 (13%)	1.00
Other	1 (2%)	5 (8%)	0.21	1 (3%)	2 (5%)	1.00	0	3 (13%)	0.23
Functional location of tumor			1.00			1.00			1.00
Eloquent	14 (23%)	20 (32%)	0.31	8 (21%)	8 (21%)	1.00	6 (26%)	12 (52%)	0.13
Near-eloquent	40 (66%)	29 (47%)	0.05	24 (63%)	20 (51%)	0.36	16 (70%)	9 (39%)	0.08
Non-eloquent	7 (11%)	13 (21%)	0.22	6 (16%)	11 (28%)	0.27	1 (4%)	2 (9%)	1.00
No. patients with direct cortical stimulation	15 (25%)	19 (31%)	0.55	8 (21%)	9 (23%)	1.00	7 (30%)	10 (44%)	0.54
Median size of tumor (range)	13.9 (0.2-108)	13.7 (0.5-119)	0.48	9.3 (0.2-108.0)	7.8 (0.5-119.1)	0.48	32.0 (1.3-102.5)	29.6 (0.6-75.3)	0.43
No. of lesions (%)			1.00			1.00			1.00
1	47 (77%)	45 (72%)	0.68	27 (71%)	24 (62%)	0.47	20 (87%)	21 (91%)	1.00
2	8 (13%)	11 (18%)	0.62	5 (13%)	9 (23%)	0.38	3 (13%)	2 (9%)	1.00
3	3 (5%)	6 (10%)	0.49	3 (8%)	6 (15%)	0.48	0	0	1.00
4	3 (5%)	0	0.12	3 (8%)	0	0.12	0	0	1.00
Extent of resection			1.00			1.00			1.00
Gross total	50 (85%)	55 (89%)	1.00	33 (94%)	37 (95%)	1.00	17 (77%)	18 (78%)	1.00
Subtotal	4 (7%)	2 (3%)	0.43	2 (6%)	0	0.22	2 (9%)	2 (9%)	1.00
Partial	3 (5%)	5 (8%)	0.72	0	2 (5%)	0.50	3 (14%)	3 (13%)	1.00

Table 2

Final histopathological diagnosis in the metastasis and glioma patient groups

Histopathological Diagnosis	Total N=77	Observe N=38	Prophylaxis N=39
Metastasis Group (primary cancer type)			
Lung	32 (41%)	17 (45%)	15 (38%)
Melanoma *	19 (25%)	5 (13%)	14 (36%)
Renal	11 (14%)	6 (16%)	5 (13%)
Breast	6 (8%)	3 (8%)	3 (8%)
Other primary	9 (12%)	7 (18%)	2 (5%)

Glioma group	Total N=46	Observe N=23	Prophylaxis N=23
High grade – Total	37 (80%)	20 (87%)	17 (74%)
Grade IV (GBM)	31 (67%)	17 (74%)	14 (61%)
Grade III (Anaplastic)	6 (13%)	3 (13%)	3 (13%)
Low grade gliomas	6 (13%)	2 (9%)	4 (17%)
Non-glioma **	3 (7%)	1 (4%)	2 (9%)

* p< 0.05 (chi square Fischer exact test)

** Pathology included: metastasis, lymphoma, and T-cell lymphoproliferative disorder.

Table 3

Comparison of seizure events

	Whole Group Observe N=61	Prophylaxis N=62	p- value	Metastasis Subgroup Observe N=38	Prophylaxis N=39	p- value	Glioma Subgroup Observe N=23	Prophylaxis N=23	p- value
All seizure events	11 (18%)	15 (24%)	0.51	5 (13%)	6 (15%)	1.00	6 (26%)	9 (39%)	0.53
Early seizure (<30 days)	5 (8%)	6 (10%)	1.00	2 (5%)	1 (3%)	0.62	3 (13%)	5 (22%)	0.70
Within 24 hours	2 (3%)	1 (2%)	0.62	1 (3%)	0 (0%)	0.49	1 (4%)	1 (4%)	1.00
Within 3 days	3 (5%)	2 (3%)	0.68	1 (3%)	0 (0%)	0.49	2 (9%)	2 (9%)	1.00
Seizure < 1 week	5 (8%)	2 (3%)	0.27	2 (5%)	0 (0%)	0.24	3 (13%)	2 (9%)	1.00
Early clinically significant	2 (3%)	1 (2%)	0.62	1 (3%)	0 (0%)	0.49	1 (4%)	1 (4%)	1.00
Late (> 30 days)	6 (10%)	9 (14%)	0.58	3 (8%)	5 (13%)	0.71	3 (13%)	4 (17%)	1.00
Seizure Type									
Generalized	5 (46%)	5 (33%)	1.00	2 (40%)	2 (33%)	1.00	3 (50%)	3 (33%)	1.00
Focal	4 (36%)	8 (53%)	0.36	2 (40%)	3 (50%)	1.00	2 (33%)	5 (56%)	0.41
Complex Partial	0	1 (7%)	1.00	0	0		0	1 (11%)	1.00
Other	2 (18%)	1 (7%)	0.62	1 (20%)	1 (17%)	1.00	1 (17%)	0	1.00

Table 4

Percentage of patients with subtherapeutic, therapeutic, or toxic serum levels of prophylaxis in group randomized to receive prophylaxis during 7-day period

Prophylaxis Level (mg/l)	Observation time point (Number of patients observed)								
	Day 0 (48)	POD 1 (56)	POD 2 (50)	POD 3 (44)	POD 4 (17)	POD 5 (8)	POD 6 (6)	POD 7 (9)	POD 8 (27)
0-5	6%	0%	0%	2%	0%	0%	17%	0%	56%
5-10	15%	11%	6%	21%	18%	12%	17%	0%	18%
10-20	77%	84%	82%	77%	82%	88%	66%	100%	26%
20-30	2%	5%	12%	0%	0%	0%	0%	0%	0%

* Therapeutic drug level: 10-20 mg/L

Table 5

Comparison of adverse events within 30 days

	Whole Group		p-value	Metastasis Subgroup		p-value	Glioma Subgroup		p-value
	Observe N=61	Prophylaxis N=62		Observe N=38	Prophylaxis N=39		Observe N=23	Prophylaxis N=23	
Total No. AEs	** 0 (0%)	11 (18%)	<0.01	0 (0%)	7 (18%)	0.01	0 (0%)	4 (17%)	0.11
Major [*]	0 (0%)	3 (5%)	0.24	0 (0%)	2 (5%)	0.49	0 (0%)	1 (4%)	1.00
Minor [*]	0 (0%)	9 (15%)	<0.01	0 (0%)	5 (13%)	0.06	0 (0%)	4 (17%)	0.11

^{*} 1 patient had both minor and major events^{**} AE = Adverse Events