Seizures constitute very serious complications of brain tumor surgery as they often delay recovery and even cause death. Seizures occur in 20 to 40 percent of patients with brain tumors (1, 2). Frontal and parietal tumor location is more likely to be associated with seizures, as are slowly growing tumors (3). Craniotomies or biopsies, often done for diagnoses, may also increase risk of seizures. Previous retrospective studies reported no significant reduction of seizure incidence with prophylactic antiepileptic medications in patients with supratentorial gliomas (4) and provided conflicting results on the role of seizure prophylaxis in patients with metastatic brain tumors (1). On the other hand, prospective studies have not specifically recruited patients with gliomas or metastatic supratentorial tumors needing craniotomy to study the efficacy of antiepileptic drug (AED) prophylaxis in reducing postoperative seizures. Such studies either focused on brain tumor patients with or without craniotomy (2), or on craniotomy patients with or without brain tumors (5). Thus, the debate continues about seizure prophylaxis after craniotomy for intraparenchymal tumor resection.

Wu et al. conducted a prospective randomized trial in patients with intraparenchymal brain tumors undergoing craniotomy to examine the use of phenytoin for postoperative seizure prevention (6). Eligible patients were ones with primary or metastatic supratentorial brain tumors who had not had seizures prior to surgery. They were randomized to a 7-day
phenytoin therapy versus observation without AED treatment, and the endpoints were seizure occurrence and adverse reactions to phenytoin. Subjects in the treatment arm received intravenous loading with 15 mg/Kg of phenytoin in the operating room right before craniotomy, and were started on 100 mg every 8 hours orally or intravenously, with adjustments as needed to keep serum levels between 10 and 20 mg/L.

The study was done over 6 years at a single center. Initially, the power analysis estimated 142 patients divided equally over treatment and control arms would be needed to detect a significant (Type I error of 0.05) seizure reduction of two-thirds from an estimated seizure incidence of 30% in the observation arm to 10% in the treatment arm. The trial, however, was closed after recruiting 123 subjects—that is, 9 subjects short of the target—because a predictive probability analysis concluded that continued accrual will find no difference in seizure incidence between treatment and control arms. This was due to the low incidence of seizures in the control arm: Only 8% had seizures in the first month, compared with 10% in the phenytoin group (p = 1.0). Over the whole observation period, seizure incidence was 18% in the observation group and 24% in the phenytoin group (p = 0.51). There was also no difference in the incidence of clinically significant early seizures between the 2 groups (0.62), but the phenytoin group experienced more adverse events than controls (p < 0.01), as expected.

The findings of this study are consistent with previous randomized trials of prophylactic AEDs in patients with brain tumors that found no benefit of prophylaxis in preventing seizures (1, 2). There are many strengths in this study: First, it might be the only prospective randomized clinical trial to address the question of prophylactic antiepileptic therapy in patients undergoing craniotomy for brain tumors without a history of previous seizures. Second, the randomization was optimal as the 2 arms of the study were very adequately comparable in terms of the tumor size, functional location, tumor size, number of lesions, extent of resection, and demographic variables. A very important finding in the current study was the lower seizure incidence in the observation group than previously expected, as other studies had reported up to 40% chance of seizures in patients with brain tumors (2). Phenytoin withdrawal is unlikely to have resulted in increased seizures in the treatment arm, although a trend could be seen toward that effect: During the latter 3 weeks of the first month—which included the taper (one week) and discontinuation (2 weeks) of phenytoin—4 patients in the phenytoin arm had seizures compared with none in the observation group (p = 0.12, Fisher’s exact test).

Levetiracetam and other antiepileptic drugs that do not have major interactions with other medications and have more tolerable adverse event profiles would be more appropriate choices than phenytoin for future trials, especially since most AEDs probably have comparable efficacy (7). For example, in patients undergoing radiation therapy, phenytoin can increase the risk of erythema multiforme (8, 9), which resulted in an exclusion criteria in the current study. In addition, phenytoin requires frequent serum level assessments, it is prone to interact with other medications, notably chemotherapeutic agents and antibiotics, and it has a high incidence of adverse events. In the current study, for example, a total of 20 adverse events occurred in 61 patients, including 5 major adverse events. Thus, future trials should use AEDs that are also available in intravenous and oral formulations but have better adverse event profile, linear pharmacokinetics, no interactions with other drugs, rapid onset of action, are renally excreted, and 100% bioavailable. In addition, phenytoin is not as safe for the fetus during pregnancy as levetiracetam (10). Moreover, if future studies are to address the antiepileptogenic potential of seizure prophylaxis (by administering them shortly after craniotomy and then assessing whether seizure incidence is reduced upon longitudinal follow up after AED discontinuation), then the appropriate treatment duration that results in the best outcome should also be identified.

by Mohamad Koubeissi, MD

References

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

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4. Other relationships
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**Disclosure of Potential Conflicts of Interest**

**Section #1 Identifying Information**

1. **Today’s Date:** 6/12/2012

2. **First Name** Mohamad  
   **Last Name** Koubeissi  
   **Degree** MD

3. Are you the Main Assigned Author?  
   ☒ Yes  
   ☐ No

   If no, enter your name as co-author:

4. **Manuscript/Article Title:** Do We Need Seizure Prophylaxis for Brain Tumor Surgery?

5. **Journal Issue you are submitting for:** 14.1

**Section #2 The Work Under Consideration for Publication**

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

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<th>Money to Your Institution*</th>
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* This means money that your institution received for your efforts on this study.

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**Section #4 Other relationships**

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